20 October 2011
EMA/CHMP/484377/2011
Committee for Medicinal Products for Human Use (CHMP)

# CHMP assessment report

**Ameluz**

International non-proprietary name: **5-aminolaevulinic acid**

Procedure No. **EMEA/H/C/002204**

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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# Product information

| | |
|---|---|
| **Name of the medicinal product:** | Ameluz |
| **Applicant:** | Biofrontera Bioscience GmbH<br>Hemmelrather Weg 201<br>D-51377 Leverkusen<br>Germany |
| **Active substance:** | 5-aminolaevulinic acid hydrochloride |
| **International Non-proprietary Name/Common Name:** | 5-aminolaevulinic acid |
| **Pharmaco-therapeutic group (ATC Code):** | Sensitizers used in photodynamic/radiation therapy (L01XD04) |
| **Therapeutic indication:** | Treatment of actinic keratosis of mild to moderate intensity on the face and scalp (Olsen grade 1 to 2; see section 5.1) |
| **Pharmaceutical form:** | Gel |
| **Strength:** | 78 mg/g |
| **Route of administration:** | Cutaneous use |
| **Packaging:** | tube (alu) |
| **Package size:** | 1 tube |

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# List of abbreviations

| | |
|---|---|
| % | percent |
| ∞ | infinity |
| $^1O_2$ | singlet oxygen |
| 5-FU | 5-fluorouracil |
| A1 | alternative hypothesis |
| AE | adverse event |
| AK | actinic keratosis |
| ALA | 5-aminolaevulinic acid |
| ALAD | aminolaevulinic acid dehydratase |
| ATP | adenosine triphosphate |
| BMI | body mass index |
| $\chi 2$ | chi square |
| C | Caucasian |
| CCCR | complete clinical clearance rate |
| CI | confidence interval |
| cm | centimetre |
| $cm^2$ | square centimetre |
| CHMP | Committee for Human Medicinal Products |
| CR | clearance rate |
| EC | Ethics committee |
| e.g. *exempli gratia*, | for example |
| EMA | European Medicines Agency |
| EU | European Union |
| F | women |
| FAS | full-analysis set |
| g | gram |
| µg | microgram |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| H | hour |
| H0 | null hypothesis |
| H1 | (alternative) hypothesis |
| HIV | Human immunodeficiency virus |
| ICH | International Conference on Harmonization |
| i.e. | *id est*, that is |
| ITT | intent-to-treat |
| J | Joule |
| kg | kilogram |
| LOCF | last observation carried forward |
| M | men |
| $m^2$ | square meter |
| mm | millimetre |
| $mm^2$ | square millimetre |
| MAL | methyl-aminolaevulinic acid |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram |
| µg | microgram |
| mL | millilitre |
| mW | milliwatt |
| n | number |
| N/A | not applicable |
| nm | nanometre |
| OR | odds ratio |
| *P* | probability |
| PBG | porpobilinogen |
| PDT | photodynamic therapy |
| PK | pharmacokinetics |
| PP | per-protocol |
| PpIX | protoporphyrin IX |
| r | randomized |

| | |
|---|---|
| Resp | Respectively |
| ROS | reactive oxygen species |
| sec | second |
| SCC | squamous cell carcinoma |
| SD | standard deviation |
| SK | solar keratosis |
| SmPC | Summary of Product Characteristics |
| Target area A | face and forehead |
| Target area B | bald scalp |
| TEAE | treatment emergent adverse event |
| U | unit |
| UV | ultraviolet |
| vs. | *versus*, as opposed to |

# 1. Background information on the procedure

## *1.1 Submission of the dossier*

The applicant Biofrontera Bioscience GmbH submitted on 2 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ameluz, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2008. The eligibility to the centralised procedure under Article 3(2) (b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The applicant applied for the following indication: treatment of actinic keratosis of mild to moderate intensity on the face and scalp (Olsen grade 1 to 2).

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

## *Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/157/2009 on the granting of a (product-specific) waiver.

## *Information relating to orphan market exclusivity*

**Similarity**

Not applicable.

## *Scientific Advice*

The applicant did not seek scientific advice at the CHMP.

## *Licensing status*

The product was not licensed in any country at the time of submission of the application.

### *1.2 Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Harald Enzmann** Co-Rapporteur: **Patrick Salmon**

- The application was received by the EMA on 2 September 2010.
- The procedure started on 22 September 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 December 2010. The Co-Reporter's first Assessment Report was circulated to all CHMP members on 13 December 2010.
- During the meeting on 17-20 January 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 January 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 July 2011.
- During the CHMP meeting on 21 July 2011, the CHMP agreed on a List of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 September 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 6 October 2011.
- During the meeting on 17-20 October 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ameluz on 20 October 2011.

# 2. Scientific discussion

### *2.1 Introduction*

## Problem statement

Actinic keratosis (AK) is an ultraviolet-light-induced lesion of the skin that may progress to invasive squamous cell carcinoma (Glogau, 2000). It is the most common lesion with malignant potential to arise on the skin. AK is mostly seen in fair-skinned persons on skin areas that have had long-term sun exposure (Salasche, 2000).

Epidemiological data show a high occurrence rate of AK. Regions with higher ultraviolet exposure have a higher prevalence of AK. In Europe, a prevalence of 15% in men and 6% in women has been documented. Over the age of 70 years, 34% of men and 18% of women were found to have AK (Memon et al., 2000).

An AK may regress, persist unchanged, or progress to invasive squamous cell carcinoma. The actual percentage that progress to invasive SCC remains unknown, and estimates vary from 5% to 20% within 10 to 25 years with reported annual transformation rate ranging widely from as low as 0.25% to

as high as 16% (Braathen et al., 2007). Furthermore, predicting which course each individual lesion will follow is impossible.

AK treatment options belong to 2 broad categories: surgical destruction of the lesions (e.g. using cryosurgery or curettage with or without electrosurgery) and medical therapy. Medicinal products approved in the EU include 5-fluorouracil cream, imiquimod cream, diclofenac gel, and photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) or methyl-aminolaevulinic acid (MAL).

Two products containing ALA or ALA derivates have been available since several years. The two ALA-PDT products use different ways to address the problem around the inherent instability of ALA in aqueous formulations. Levulan is provided as a 2-component system to be mixed immediately before use, ALAcare takes advantage of the attachment of solid ALA crystals to the plaster (Hauschild et al., 2009) and Metvix uses the more stable methyl-ester derivative MAL.

A second drawback is the fact that ALA is a dipolar ion at physiologic pH with low lipid solubility and limited ability to penetrate the stratum corneum. The use of more lipophilic ALA derivatives such as MAL is an attempt to overcome this problem, but skin penetration is only improved with esters with an even higher number of carbon ions (≥C4). Short-chained ALA-esters (C1-C3) induced 5 to 10 times lower PpIX accumulation than ALA as shown in several cell lines (Gaullier et al., 1997).

The rationale to develop Ameluz was to provide a novel ALA formulation for PDT which increases the stability of the active ingredient and improves the delivery of the active ingredient into the target cells of the AK lesions within the epidermis.

## About the product

Ameluz (known as BF-200 ALA) is a gel formulation containing ALA in a nanoemulsion developed for topical treatment of actinic AK in combination with PDT. The nanoemulsion formulation provides chemical stabilization of ALA and enhances its penetration into the epidermis.

Following topical application of 5-aminolaevulinic acid, the substance is metabolized to protoporphyrin IX, a photoactive compound which accumulates intracellularly in the treated actinic keratosis lesions. Protoporphyrin IX is activated by illumination with red light of a suitable wavelength and energy. In the presence of oxygen, reactive oxygen species are formed. The latter causes damage of cellular components and eventually destroys the target cells.

The Applicant applied for the indication: Treatment of actinic keratosis of mild to moderate intensity on the face and scalp (Olsen grade 1 to 2). The finally approved indication was: Treatment of actinic keratosis of mild to moderate intensity on the face and scalp (Olsen grade 1 to 2; see section 5.1 of the SmPC).

The gel should cover the lesions and approximately 5 mm of the surrounding area with a film of about 1 mm thickness. The entire treatment area will be illuminated with a red light source, either with a narrow spectrum around 630 nm and a light dose of approximately 37 J/cm$^2$ or a broader and continuous spectrum in the range between 570 and 670 nm with a light dose between 75 and 200 J/cm$^2$.

One session of photodynamic therapy should be administered for single or multiple lesions. Actinic keratosis lesions should be evaluated three months after treatment. Non- or partially responding lesions should be re-treated in a second session. The gel should cover the lesions and approximately 5 mm of the surrounding area with a film of about 1 mm thickness. The entire treatment area will be illuminated with a red light source, either with a narrow spectrum around 630 nm and a light dose of approximately 37 J/cm$^2$ or a broader and continuous spectrum in the range between 570 and 670 nm with a light dose between 75 and 200 J/cm$^2$. It is important to ensure that the correct light dose is

administered. The light dose is determined by factors such as the size of the light field, the distance between lamp and skin surface, and the illumination time. These factors vary with lamp type. The light dose delivered should be monitored if a suitable detector is available.

Before administration of Ameluz scales and crusts should be removed accurately. In addition, all lesion surfaces should be roughened gently. Care should be taken to avoid bleeding. Thereafter, all lesions should be carefully wiped-off with an ethanol or isopropanol-soaked cotton pad to ascertain degreasing of the skin.

Ameluz should be applied to the entire lesion area using glove protected fingertips or a spatula. The gel can be administered to healthy skin around the lesions, whereas application near the eyes, nostrils, mouth, ears or mucosa should be avoided (keep a distance of 1 cm). Direct contact of Ameluz with the eyes or mucous membrane should be avoided. In case of accidental contact, rinsing with water is recommended. The gel should be allowed to dry for approximately 10 minutes, before an occlusive light-tight dressing is placed over the treatment site. Following 3 hours of incubation, the dressing should be removed and the remnant gel wiped off.

Immediately after cleaning the lesions, the entire treatment area will be illuminated with a red light source. During illumination the lamp should be fixed at the distance from the skin surface that is indicated in the user manual. A narrow spectrum lamp is recommended to achieve higher clearance rates. Symptomatic treatment of transient adverse site reactions may be considered. A broader and continuous spectrum may be used if narrow-spectrum light sources are not tolerated.

Lesions should be re-assessed after three months, at which point any residual lesions may be retreated.

## *2.2 Quality aspects*

### 2.2.1 Introduction

Ameluz 78mg/g is a gel for cutaneous use, presented in a 2g tube, for the photodynamic treatment of actinic keratosis of mild to moderate intensity on the face and scalp. The active substance, is 5-aminolaevulinic acid (as 5-aminolaevulinic acid hydrochloride), which is of synthetic chemical origin.

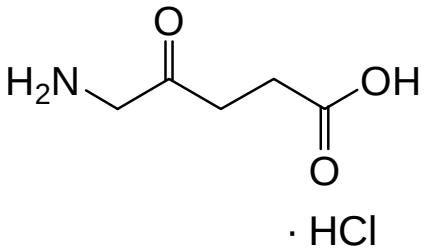
Ameluz is a white to yellowish gel containing 78mg/g of 5-aminolaevulinic acid (as hydrochloride) filled in aluminium tubes with epoxyphenol inner lacquer and a latex seal and a screw cap of high density polyethylene.

The excipients used in the preparation of Ameluz are xanthan gum, soybean phosphatidylcholine, polysorbate 80, medium-chain triglycerides, isopropyl alcohol, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, propylene glycol, sodium benzoate and purified water.

The gel is intended to be applied to prepared skin lesions and covered with an occlusive dressing to aid absorption. The gel contains an o/w nanoemulsion which enhances skin penetration of the active substance. The active substance is metabolised within the dermis to protoporphyrin IX which accumulates intracellularly within the actinic keratosis lesion. The photoactive protoporphyrin IX is then activated by a defined CE-marked red-light source to produce reactive oxygen species which destroy the target cells to produce the required effect.

### 2.2.2 Active Substance

The active substance is 5-aminolaevulinic acid hydrochloride, an achiral substance which is crystalline and readily soluble in water, ethanol and dimethylformamide. The active substance is not covered by a pharmacopoeial monograph. The figure below shows the chemical structure of 5-aminolaevulinic acid hydrochloride.




The octanol/water partition coefficient (P) illustrates the hydrophile/lipophile balance of 5-aminolaevulinic acid and has been experimentally determined as 0.03. The log P value is -1.5. No specific permeability studies have been carried out for 5-aminolaevulinic acid, however, the partition coefficient between the stratum corneum and water (KSC/W) was determined to be 0.04 (log KSC/W -1.37). The partition coefficient and corresponding log P values determined for 5-aminolaevulinic acid for octanol/water and stratum corneum/water reflect the high water solubility of 5-aminolaevulinic acid.

## *Manufacture*

5-Aminolaevulinic acid hydrochloride is manufactured in two steps from 5N-(phthaloyl) amino-laevulinic acid methyl ester, consisting of ester hydrolysis and recrystalllisation of crude 5-aminolaevulinic acid hydrochloride. A description of the manufacture and a list of materials used for manufacture of 5N-(phthaloyl)amino-laevulinic acid methyl ester as well as the specification of laevulinic acid and the intermediate of the synthesis of 5N-(phthaloyl)amino-laevulinic acid methyl ester have been provided, the starting material should be redefined. A request has been included in the list of recommendations.

Details on the control of the materials used, both for manufacture of 5N-(phthaloyl)amino-laevulinic acid methyl ester and the final active substance, including specifications for raw materials and details and justification of the control of the starting material including analytical methods and validation were satisfactorily provided. Details were also provided on critical in-process tests during manufacture together with control limits during manufacture and validation of analytical methods.

The results from 1H-NMR and 13C-NMR spectra, elemental analysis and the mass spectrum are consistent with the structure of the active substance.

Synthesis related impurities, degradation pathways and residual solvents were satisfactorily presented.

Batch results were presented for six production scale batches and one pilot scale batch. All batch results are in accordance with the specification of 5-aminolaevulinic acid hydrochloride.

## *Specification*

The active substance specification includes tests for description (visual examination), identification (IR spectroscopy, HPLC, test on chloride and melting point), assay (HPLC and argentometric), related substances (HPLC), water content (Karl Fisher), loss on drying (Ph.Eur.), sulphated ash (Ph.Eur.) and residual solvents (GC).

The specification was found to be justified. Impurities have been evaluated and found to be acceptable from the point of view of safety. However, based on batch data results, the limit for the sum of total impurities should be further tightened once further batch experience is gained. This request is included in the list of recommendations.

All analytical procedures of the active substance were described and were generally sufficiently validated. However, a request for a full validation of the HPLC method applied for the control of impurities in the starting material, 5N-(phthaloyl) amino-laevulinic acid methyl ester, is included in the list of recommendations.

The finished product manufacturer controls the active substance according to the specification and analytical procedures of the active substance manufacturer.

Validation in line with ICH requirements has been carried out for the HPLC method. The validation included specificity for impurities from the active substance specification and those arising in the active substance starting material. The HPLC method was found to be stability indicating as it is able to detect impurities arising out of forced degradation. Range, linearity and accuracy have been determined for the active and specified impurities of the active substance specification. The ranges studied are appropriate for assay and known impurities respectively. Linearity, accuracy and repeatability of the assay of 5-aminolaevulinic acid were validated from 80 to 120% of label claim. Intermediate precision was verified at 100% of the active substance.

Batch analytical data provided on six production scale batches demonstrated compliance with the specification and showed the active to be of good quality.

Impurities have been evaluated and found to be acceptable from the point of view of safety.

The reference standards for 5-aminolaevulinic acid were presented in adequate detail. Identity and purity of the impurity reference standards were sufficiently characterized. There is a remaining point for clarification regarding standards for two unspecified impurities which is included in the list of recommendations.

### *Stability*

Long-term stability studies at -15°C, at 5°C and at 25 °C / 60% RH were performed on three production scale batches for 36 months. Storage at 40°C/75% RH (accelerated conditions) for 12 months led to discoloration of the active substance and to out of specification results of related substances.

The stability studies showed that the active substance is stable when stored in a freezer and confirm the proposed re-test period.

### *Comparability exercise for Active Substance*

Not applicable.

## 2.2.3 Finished Medicinal Product

Ameluz is a non-sterile gel formulation for the topical treatment of actinic keratosis lesions. It is presented in aluminium tubes with epoxyphenol inner lacquer and latex seals which are closed with screw caps made of high density polyethylene. The product is intended for single use and each tube contains 2g of gel. Ameluz 78mg/g gel contains 7.8% of 5-aminolaevulinic acid which is equivalent to 10% of 5-aminolaevulinic acid hydrochloride salt.

### *Pharmaceutical Development*

The active substance is hydrophilic, unstable in aqueous solutions and has limited ability to penetrate the outer epidermal layer (stratum corneum) which is more permeable for lipophilic compounds.

The objective of the pharmaceutical development was to provide a novel formulation of 5-aminolaevulinic acid, which increases the stability and improves the delivery of the active substance through the stratum corneum and into the target cells of the lesions of actinic keratosis within the epidermis.

A gel formulation was selected, containing a nanoscale oil in water emulsion. Soybean phosphatidylcholine-containing nanoemulsions are able to stabilize 5-aminolaevulinic acid in the gel, significantly contributes to the enhancement of the permeation of 5-aminolaevulinic acid through the skin. Soybean-derived phospholipids have high affinities to epidermal tissue and change the skin lipid fluidity leading to enhanced percutaneous drug absorption. Therefore, it is possible to reduce the concentration of the active ingredient, while maintaining an efficient uptake of the active substance into neoplastic cells.

The data submitted suggested that 5-aminolaevulinic acid is not included in the nanoemulsion core. 5-Aminolaevulinic acid is a strongly hydrophilic molecule. Therefore, it is not expected that 5-aminolaevulinic acid is included in the core of the nanoemulsion. Further, indirect evidence is provided by the cell culture experiments, which have shown that the uptake of 5-aminolaevulinic acid in cell culture is also increased when the nanoemulsion and 5-aminolaevulinic acid are added successively, indicating that the effect is not the consequence of a direct interaction of the nanoemulsion and 5-aminolaevulinic acid.

The excipients used in the preparation of Ameluz are xanthan gum (gel forming agent), soybean phosphatidylcholine (surfactant), polysorbate 80 (co-surfactant), medium-chain triglycerides (lipid core), isopropyl alcohol (solvent), disodium phosphate dehydrate (buffering agent), sodium dihydrogen phosphate dehydrate (buffering agent), propylene glycol (solvent), sodium benzoate (preservative) and purified water (solvent). All excipients are of Ph. Eur. quality with exception of soybean phosphatidylcholine which is controlled for identity, purity and assay with an in-house monograph.

The antimicrobial effectiveness of the preservative has been confirmed and complies with Ph. Eur. 5.1.3 criteria A.

### *Adventitious agents*

None of the excipients used in the formulation of Ameluz are of animal origin.

### *Manufacture of the product*

The manufacturing process of Ameluz comprises (1) preparation of an aqueous buffer phase, (2) preparation of the gel phase, (3) preparation of the nanoemulsion, (4) preparation of the bulk product by adding the preservative, the active substance and the gel phase, (5) filling into aluminium tubes and secondary packaging.

The critical quality attributes of the drug product appear to be the particle size and viscosity. The physico-chemical characterization of the drug product, including characterization of the particle size distribution by photon correlation spectroscopy and electron microscopy, has been sufficiently detailed.

There are several in process controls such as determination of the pH of the buffer, viscosity of the gel phase, pH, particle size and size distribution of the nanoemulsion and the bulk product, check of the fill weight at the end of the filling operation. All parameters of the release specification were analysed. The results indicated homogeneity of macroscopic appearance, pH, viscosity, assay of active substance, content of preservative, related substances (specified impurities below 0.1%, unspecified impurities at or below 0.1%, respectively), microbial purity and filling weight. Intra-batch homogeneity of the nanoparticle size distribution has been confirmed on a fourth process validation batch.

Nonetheless, further data should be generated documenting intra-batch homogeneity with regard to the particle size of the nanovesicles for the first two batches to be manufactured after granting of the marketing authorisation. This request is included in the list of recommendations.

Three full scale batches were manufactured using the same manufacturing facilities, manufacturing process and same equipment as the batches intended for marketing. The batches fully met the quality control specifications, and results of IPC and additional testing show that the manufacturing process is robust. Each of the drug product batches was manufactured with a different batch of the drug substance. Therefore it can be concluded that the batches can be manufactured reproducibly at commercial scale.

### *Product specification*

The specification for Ameluz includes tests for appearance (visual examination), identification of 5-aminolaevulinic acid (HPLC and TLC), identification of sodium benzoate (HPLC), assay of 5-aminolaevulinic acid and sodium benzoate (HPLC), extractable mass, pH (Ph.Eur.), viscosity (vibroviscosimetry), particle size (laser light scattering), related substances (HPLC-MS) and microbial purity (Ph.Eur.).

The release and shelf-life specification for the drug product were found to be justified. However, based on batch data results, the limit for the sum of total impurities should be further tightened in line with long term stability results. In addition, the shelf life limit for a specified impurity should be tightened when further batch data become available. These requests are included in the list of recommendations.

All methods have been satisfactorily validated. The HPLC method has been validated for specificity, linearity, range, accuracy, intermediate precision and robustness. The validation data demonstrated that the method is suitable for the identification and assay test of 5-aminolaevulinic acid hydrochloride. For methods described in the Ph. Eur. validation was deemed to be unnecessary. The microbial purity of the drug product was compliant with Ph. Eur. requirements for preparations for cutaneous use.

### *Stability of the product*

The stability of the drug product has been investigated with three production scale batches from the manufacturer proposed for marketing. The batches were stored in the packaging as proposed for manufacture in accordance with the requirements of the ICH stability guideline ICH Q1A (R2). Long-term stability data (5°C) for 24 months showed no significant change in the product quality. Storage at 25°C, 30°C and 40°C resulted in out of specification results.

The stability results support the shelf life and storage conditions as defined in the SPC

### *Comparability Exercise for Finished Medicinal Drug Product*

Not applicable

## GMO

Not applicable

### 2.2.4 Discussion on chemical, pharmaceutical and biological aspects

The active substance and finished product have been adequately described. The excipients used in the preparation of the finished product and the manufacturing process selected are typical of a cutaneous preparation. The results of the tests indicate that the active substance and the finished product can be reproducibility manufactured and therefore the product should have a satisfactory and uniform performance.

### 2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### 2.2.6 Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The Committee recommends to re-define the starting material further back and to implement the GMP requirements at an earlier stage of the synthesis of the active substance.

2. The Committee recommends determining the limit of quantitation for the GC method used to control impurities of the redefined starting material.

3. The Committee recommends that the applicant fully validates the HPLC method for control of impurities in the starting material, 5-N-(phthaloyl)-aminolaevulinic acid methyl ester, in accordance with the agreed validation plan

4. The Committee recommends tightening the limit for the sum of total impurities in the active substance in light of further experience and based on the results obtained form batch analysis.

5. The Committee recommends further verification of the purity of reference standards for impurities by determining their chromatographic purity.

6. The Committee recommends that the applicant generate data documenting the intra-batch homogeneity with regard to the particle size of nanovesicles for the first two batches of the finished product manufactured after granting the Community marketing authorisation.

7. The Committee recommends tightening the limit for the sum of total impurities in the finished product specification in accordance with results from the long-term stability studies at 5°C.

8. The Committee recommends revision and tightening of the limit for a specified impurity in the finished product specification when the results from the ongoing stability program are available.

## *2.3 Non-clinical aspects*

### 2.3.1 Introduction

In support of this application, the applicant has provided a literature review that describes the mechanism of action and activity of ALA in combination with PDT as well as pharmacokinetics and toxicology given its extensive clinical experience. The non-clinical testing primarily focuses on the pharmacokinetic properties and local tolerability of the new nanoemulsion formulation.

The majority of pivotal pharmacokinetic, toxicology and local tolerance studies conducted by the applicant were stated as conducted to GLP criteria.

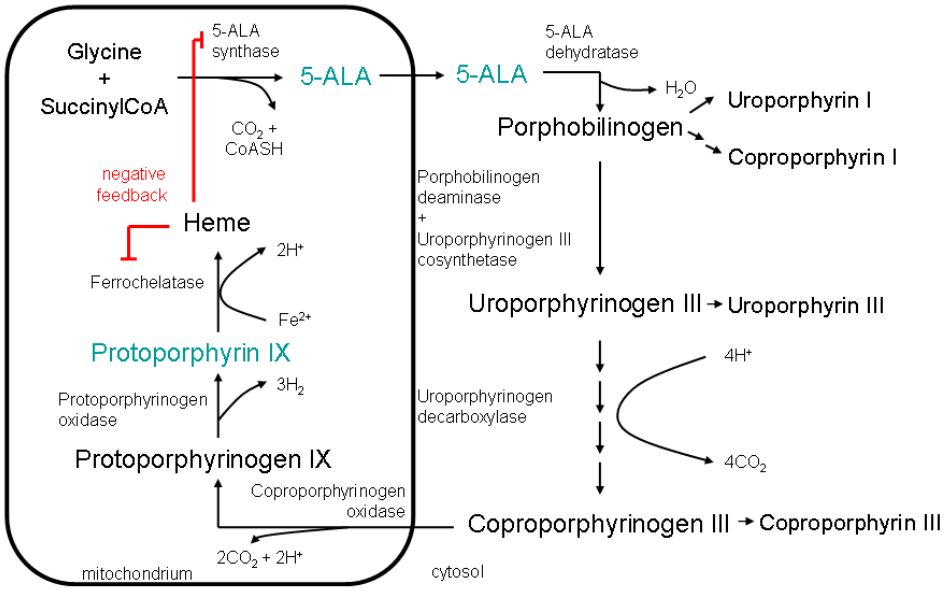
## 2.3.2 Pharmacology

### *Primary pharmacodynamic studies*

The applicant has provided an overview of the literature with respect to the mechanism of action of ALA, evidence of potential efficacy as well as known pharmacological aspects associated with ALA-PDT treatment.

Low levels of ALA as a precursor in the synthesis of heme are found in all metabolically active eukaryotic cells (Figure 1.)

**Figure 1: Pathway of Hemesynthesis (modified after Pang et al., 1997a)**




The biochemical pathway leading to heme synthesis involves the metabolism of ALA to protoporphyrin IX (PpIX), the late steps of which occur within mitochondria. The administration of ALA or MAL to fibroblasts or keratinocytes *in vitro* or to mammalian skin *in vivo* leads to an accumulation of PpIX. MAL is an ALA methyl-ester that is cleaved by cellular esterases, thereby producing ALA. Thus, the mechanism of action of MAL is identical with that of ALA with the exception of this additional metabolic step. Photodynamic therapy of AK with ALA or MAL is based on the therapeutic use of phototoxic effects induced by the illumination of accumulated PpIX. Energy from ultraviolet or visible light is first absorbed via the extensive system of conjugated double bonds in PpIX, causing a shift of the molecule from the ground state to the extremely unstable excited state.

The excited photosensitizer can react directly with tissue constituents (type I process) yielding direct or indirect cellular damage. Alternatively, cellular damage is induced through the type II process in which energy is transferred to molecular oxygen forming highly reactive $^1O_2$. The lysis of intracellular organelles caused by the reaction of $^1O_2$ with structural proteins, enzymes, protein-lipids and membranes, can subsequently trigger the release of inflammatory mediators and activate the classical complement cascade. PpIX may progress through multiple cycles of activation and energy transfer, a process that takes place in a time scale of microseconds. Since the PpIX is synthesized in mitochondria, the damage is mostly limited to these sites. Consequently, the damage occurs within a cell or at most the immediate proximity of that cell.

While slightly increased PpIX formation subsequent to ALA exposure is observed in nearly all nucleated cells, PpIX accumulation is far more pronounced (10- to 90-fold) in neoplastic cells, leading to a marked selectivity of the damage for tumour cells.

Since low levels of PpIX are present in every cell, some ROS are permanently formed during light exposure. Such minor levels are neutralized by the cell's antioxidant capacity. Based on cell culture experiments interstitial threshold-concentrations of ALA of 0.01-0.17 mg/mL have been estimated to be required to successfully eradicate lesions via the generation of PpIX in combination with illumination.

A complex interaction of several factors, including the cellular uptake of ALA and the cell's metabolic activity, may be involved in the selectivity of ALA-mediated PpIX formation. The activity of two key enzymes of the heme synthesis pathway, porphobilinogen deaminase and ferrochelatase, is changed in neoplastic cells, which could explain why PpIX accumulates in tumours and neoplastic lesions. The tumour selectivity of PDT with ALA may furthermore be due to a lower, reduced ability of tumour cells to neutralize reactive oxygen or to a reduced capacity to repair the damage caused by reactive oxygen species. After topical application of ALA the modified stratum corneum on the skin surface of AK lesions may further contribute to the selectivity of the uptake in tumour cells.

PpIX can be activated by the absorption of energy at several different wave lengths, ranging from blue to red light. Red light may be advantageous for the treatment of deeper lesions because of its better tissue penetration compared to light with shorter wave lengths. For this reason, the registered product Metvix is commonly used in combination with red light of a wavelength range around 630 nm or with a light source emitting light in the broader range between 570 and 670 nm. The same light sources have been chosen for the clinical use of Ameluz.

A photo bleaching effect of PpIX is observed during the illumination applied in PDT, leaving no detectable PpIX fluorescence within the treatment field (Kennedy et al., 1992).

The light-induced damage triggers cell death via necrosis or apoptosis, depending on the applied doses and incubation periods. Preneoplastic and neoplastic cells are eliminated and the epidermis is regenerated after healing of the induced local inflammation. Photodynamic damage, occurring mostly in mitochondria, results in the loss of the mitochondrial membrane potential and the release of proapoptotic factors (AIF, SMAC, cytochrome C) into the cytosol. This may trigger immediate necrotic cell death or the activation of caspases, resulting in apoptotic cell death.

## *Secondary pharmacodynamic studies*

- *Pain during PDT*

Investigation of PDT-induced pain was studied in two experiments designed to examine the reaction to PDT of the two cell types involved in pain generation in the skin, namely peripheral nerve endings and keratinocytes. These studies are summarised below where it appears that PDT pain is caused by two mechanisms acting in parallel.

In a secondary pharmacology study (ALA—AK-PT022) the impact of ALA-PDT on cultured dorsal root gaglion (DRG) sensory neurons of new born rats has been examined. The aim of this study was to characterise the uptake of ALA or MAL into sensory neurons and subsequently monitor calcium transients and thereby cellular activation following exposure at an ALA/PpIX level similar to that reached in the skin.

Primary sensory neuron cultures derived from newborn rat DRG were maintained for 48 h before use in the study. Prior to PDT experiments, PpIX formation was confirmed photometrically (excitation: 390 nm, emission: 620 nm) in methanol: dose-dependent increase in ALA-derived PpIX was confirmed in cell culture lysates as well as in single cells, including neurons, Schwann cells and fibroblasts. Studies disclosed sensory neurons as the main contributors of PpIX fluorescence. The effect of ALA-PDT on

sensory neurons was studied by calcium imaging. After loading the cells with 1.8 mM ALA for 30 min and a further incubation for PpIX formation for 1 h, a 10 min illumination was applied utilizing the fluorescence light source of an inverted microscope.

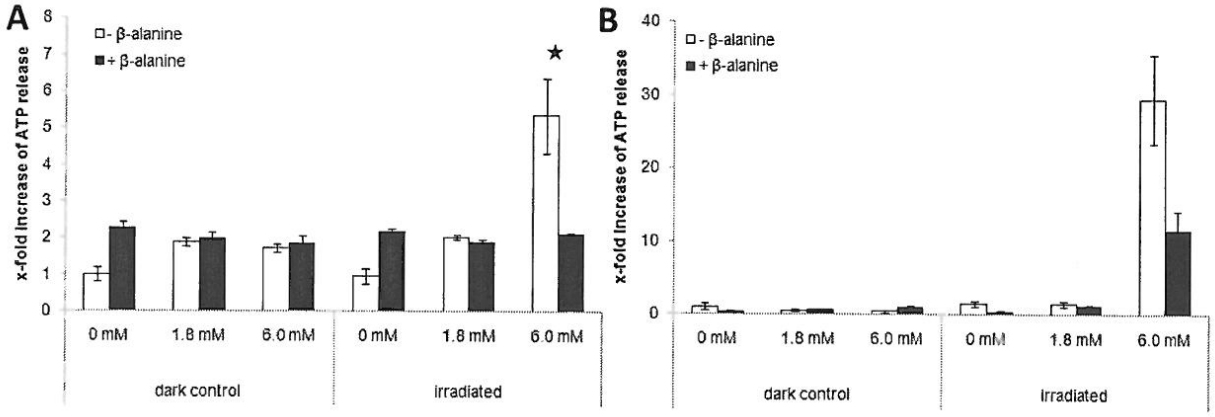
Calcium (Ca2+) imaging analysis was performed by microfluorimetric measurements of cells additionally preloaded with Fura-2/AM (3 µm; 45 min). A 10 s pulse of a depolarizing (45 mM KCl) extracellular solution was added via the application system in order to verify the neuronal identity of the cells to be recorded from. Cellular calcium was then allowed to return to baseline for another 10 min. Whenever p-trifluoromethoxyphenylhydrazone (FCCP) or thapsigargin were used (for the depletion of intracellular Ca2+ stores), their application took place during this interval. Data set was recorded after the cells had regained a stable baseline. Then the illumination program was started. Cells were superfused during illumination either by standard extracellular buffer, extracellular buffer containing calcium channel blockers, or calcium free buffer. Afterwards, a new measurement sequence was initiated. The new calcium content was recorded as dataset xII.

Illumination induced a rise in cytosolic calcium in ALA-loaded neurons to a level comparable to the depolarizing test pulse, which is 1.53 ± 0.044 compared to baseline 0.29± 0.009 w/o ALA. Neurons not previously exposed to ALA showed no alteration. Pre-depletion of calcium stores in the endoplasmic reticulum (ER) by thapsigargin (10 µM) did not alter the cellular response to PDT, ruling out the ER compartment as major Ca2+ contributor.

The second study (ALA—AK-PT023) was performed to investigate the uptake mechanisms of ALA in tumours and healthy keratinocytes and to determine if ATP is released from cells upon ALA-PDT treatment in human. ATP has been identified as a messenger molecule that can be released from keratinocytes andirritate sensory nerves. Extracellular ATP generates action potentials in the peripheral nerve fibers through binding to P2X receptors located on the nerve endings. Upon binding of ATP, P2X receptors open a cation-permeable channel, allowing sodium and calcium to flow into the cells, thereby depolarizing the membrane and triggering action potentials.

A431 cells (human squamous tumour cells) and CCD1106KERTr cells (human keratinocytes transformed with HPV-16 E6/E7) were preloaded with ALA ( 0, 1.8 and 6 mM) for 30 min. ATP release was triggered by illuminating the cells with red light for 20 min following the 4-h PpIX formation phase (lamp device: PhotoDyn (Hydrosun); equipped with a long-pass filter (BTE 41, Hydrosun), irradiation wavelength of >590 nm with an average fluence rate of 200 mW/cm2). ATP content in the medium was measured by a commercial ATP assay (CellTiterGlo), and results are shown below (Figure 2).

**Figure 2. ATP release upon irradiation in keratinocytes**




A : A431 cells and B : CCD cells

ATP release was only seen after loading with 6 mM ALA, whereas the lower dose (1.8 mM ALA) was ineffective. Inhibition of ALA uptake by ß-alanin resulted in reduced ATP release.

*Effects observed in patients with porphyria*

Porphyria has been considered a human model system of secondary pharmacological effects possibly induced by increased concentrations of ALA or PpIX. In the various extremes of porphyrias patients with increased ALA can suffer from skin photosensitization with associated burning and itching to neurotoxic effects leading to abdominal pain, peripheral neuropathy and psychiatric disturbances. Increased levels of PpIX have also been associated with skin photosentisation as well as more serious hepatic complications. However, there is evidence, that the various clinical findings reported for porphyria patients are not only related to high ALA or PpIX levels but rather to the sum of physiological changes caused by the defect in the heme pathway (Gorchein et al., 1987; Mustajoki et al., 1992).

Normal ALA concentrations in the plasma are in the range of 24-270 nmol/L. More than 30-fold higher levels of up to 9 and 12 µmol/L were reported for two cases of acute intermittent porphyria patients with overwhelming neuropathy.

The sustained infusion of high doses of ALA (50-80 mg/h) to a male volunteer for over 92.5 h induced ALA plasma levels which are normally only seen in porpyhria patients (9-12 µmol/L). However, no symptoms reported for porphyria were observed in this case (Mustajoki et al., 1992).

### *Safety pharmacology programme*

No studies were submitted (see discussion of non-clinical aspects).

### *Pharmacodynamic drug interactions*

No pharmacodynamic drug interaction studies were submitted (see discussion of non-clinical aspects).

## 2.3.3 Pharmacokinetics

The applicant reviewed general PK from literature, whereas the new experimental studies in human keratinocytes and skin (human and pig) explants focused on the properties of the new formulation Ameluz with respect to ALA uptake and tissue penetration compared to MAL (Metvix).

The *in vitro* studies focused on ALA uptake in a keratinocyte cell line of human origin (HaCat), a cell line derived from a human squamous tumour (A431), a keratinocyte cell line derived from human keratinocytes transformed with HPV-16 E6/E7 (CCD1106KERTr), and primary human keratinocytes. Then, the influence of the BF-200 nanoemulsion on the cellular uptake of ALA and the formation of PpIX was explored. It was shown that the cell penetration of ALA is enhanced in the presence of the nanoemulsion Ameluz and a time restricted influence on membrane permeability was identified.

In ex-vivo study, pig skin explants were used to investigate the penetration behaviour of Ameluz 10% in comparison to methyl-ALA ester (16% free acid corresponding to 21% ALA ester hydrochloride, Metvix cream) after topical application. The aim of the study was to evaluate the fluorescence induction of protoporphyrin IX (PpIX) as a function of time (0h, 3h, 5h, 8h, and 12h). The study showed that PpIX formation was more rapid and reached deeper regions of the epidermis after application of Ameluz gel than after Metvix at any time point tested. No PpIX formation was visible below the basal membrane at any time point. Furthermore the fluorescence in the deeper layers of the epidermis was considerably stronger for Ameluz than for Metvix cream. The basal membrane limited the extent of PpIX associated fluorescence so an undesirable effect and damage to dermal structures as a result of photoactivation of PpIX present in the dermis, and the associated risk of scarring, is not to be expected.

In order to investigate the absorption and penetration capacity of Ameluz gel in humans the applicant initiated two studies in Franz cell diffusion chambers: one study utilized fresh full thickness human skin for the administration of Ameluz 1, 3 and 10% gel; in a previous pilot study frozen human full-thickness skin was used with Ameluz 10% gel. In both studies most of the applied dose remained unabsorbed (>98% and >90%, respectively) (dislodgeable dose and stratum corneum). In the first study, the absorbed dose increased with time for all concentrations tested and showed a relatively linear dose-dependency. The absorbed dose indicated the ALA amount analysed in the receiver fluid and together with the accumulation seen in the dermis is a measure for systemic exposure. The highest absorbed dose (receiver + dermis) was found after 24 h application and was calculated at about 0.2% of the applied dose (~20 mg/cm² Ameluz 10% gel). The epidermis as relevant target area accumulated amounts of ALA that increased up to the 24 h time point. With the Ameluz 10% dose about 0.08% were present in the epidermis after 3 h and 0.15% after 24 h, respectively. In the pilot study with frozen human tissue the highest absorbed dose was seen 24 h after application of Ameluz 10% gel and no obvious correlation existed between the absorbed dose and the time after drug delivery.

Based on the results of absorption studies it was concluded that no relevant changes of endogenous ALA concentrations are expected after topical treatment with Ameluz 10% gel. This assumption was confirmed by the analysis of ALA and PpIX levels in plasma and urine samples of patients treated with Ameluz. Therefore, no kinetic studies in animals were conducted by the applicant due to the low systemic exposure expected, but data from the scientific literature provide information on the basic pharmacokinetic characteristics of ALA after IV or PO application or after instillation into the bladder.

Extensive knowledge on ALA pharmacokinetics exists in the scientific literature. Factors affecting ALA uptake were extensively studied *in vitro* and *in vivo*. As expected, ALA dose, incubation time, pH, temperature or formulation are essential parameters in this context. Exogenous ALA can be taken up and metabolized by many tissues, although the uptake and metabolization capacities may differ between different organs. Protein binding of exogenous ALA after systemic exposure was up to12%.

With topical application, no first pass metabolism is to be expected and the metabolism of ALA will take place mainly in keratinocytes. Consequently, no P-450 *in vitro* studies or studies exploring enzyme induction or inhibition were performed.

## 2.3.4 Toxicology

### *Single dose toxicity*

No single dose toxicity studies were submitted (see discussion on non-clinical aspects).

### *Repeat dose toxicity*

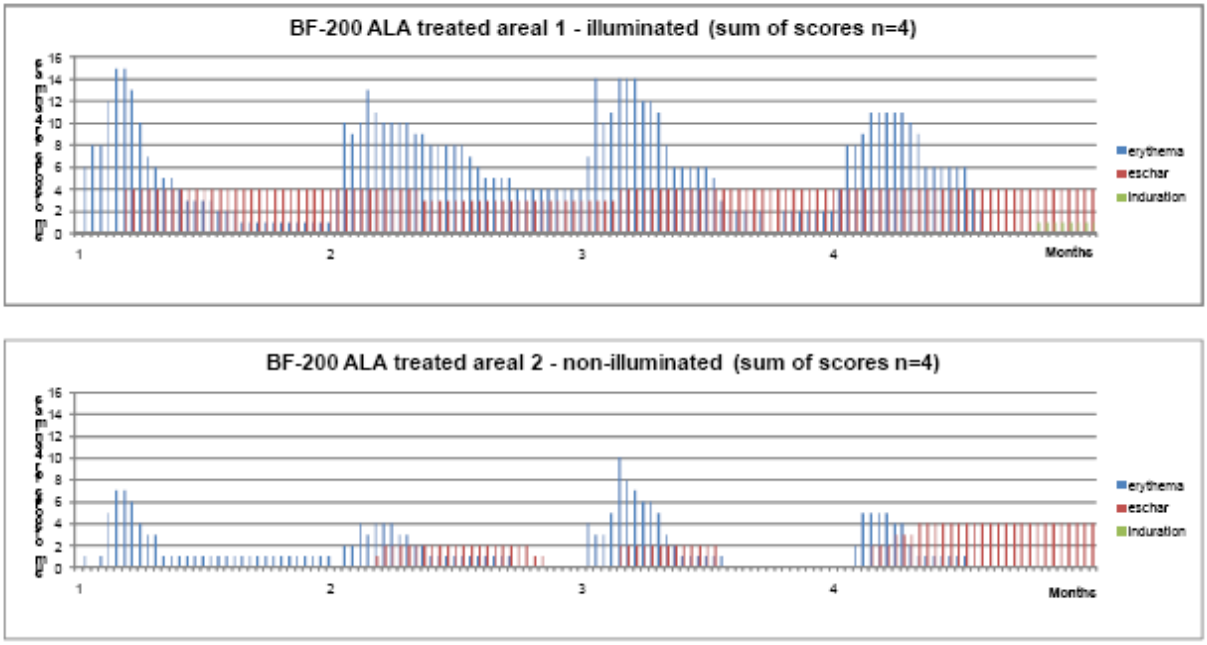
A repeat-dose dermal tolerance and toxicity study (ALA-AKPT017) was performed in mini pigs (2M, 2F). The aim of this study was to obtain information on the local and systemic toxicity of Ameluz following repeated dermal applications on minipig skin once monthly for 3 months.

Goettingen mini pigs (4-months old, 2/sex/ group) were treated with Ameluz 10% with and without PDT. Treatment and application were applied 4 times with 1-month intervals, with a recovery period of 28 days following the forth application. For histopathological assessment of the healing process, biopsies were taken on test day 88 (3 days after the last administration), test day 99 (14 days after the last administration), and test day 114 (29 days after the last administration before sacrifice).

Treatment with Ameluz with illumination resulted 3 hours after illumination in pronounced erythema (comparable to severe sunburn), lasting until the next treatment. Starting on test day 3, (slight) eschar formation was noted, and additionally indurated and thickened application site was noted for

one male animal from test day 107 onwards. Incidence and severity of these findings were more pronounced for illuminated application sites, however, some intolerance reactions were also seen on non-illuminated areas, probably due to insufficient light protection (Figure 3).

**Figure 3. Time-dependent scoring of erythema, eschar and induration after multiple ALA treatments**




Examples of ALA-treated sites with (areal 1, upper panel) and without PDT (areal 2, lower panel). Bars indicate the sum of scores from 4 animals along a time scale of up to 114 days. Repeated application is indicated on the x-axis (month 1 to 4).

No edema formation was noted. No aggravation of symptoms was noted during the course of the study.

Histopathology revealed a mild to moderate superficial purulent dermatitis with inflammatory reactions in the dermis on day 88 (3-days after the last administration). The intensity of these changes decreased on test day 99 and even further by day 114. The morphological structure of the skin treated with Ameluz 10% and illuminated was comparable to placebo-treated skin 29 days after the last application. No obvious differences were noted between males and females (Table 1).

**Table 1: Summary of the histological severity (mean values of males and females combined)**

| | Treated day biopsies were taken | | | |
|---|---|---|---|---|
| Treated area | TD 88 | TD99 | TD114 | TD114 |
| Verum with illumination | 13.64 | 7.52 | 2.01 | 4.01 |
| Verum without illumination | 13.40 | 3.25 | 2.76 | 2.00 |
| Placebo with illumination | 1.26 | 1.26 | 0.00 | 1.00 |
| Placebo without illumination | 0.88 | 1.26 | 2.00 | 0.00 |

## *Genotoxicity*

No genotoxicity studies were submitted (see discussion of non-clinical aspects).

## *Carcinogenicity*

No carcinogenicity studies were submitted (see discussion of non-clinical aspects).

## *Reproduction Toxicity*

No studies on reproductive toxicity were submitted (see discussion of non-clinical aspects).

## *Local Tolerance*

Local tolerance studies were explored in the following species: mice, rabbits and minipigs. Results of local tolerance studies are summarised in table 2.

**Table 2. Local tolerance studies performed with BF-200 ALA**

| Species/Strain: | Gender and No. per Group Method of Administration | Duration of Dosing | Doses (mg/kg) | Noteworthy Findings | Study No./ Reference: |
|---|---|---|---|---|---|
| CRL:KBL(NZW)BR rabbits (GLP) | 5F Topical | -4 h | 80 mg ALA HCl/cm² (0.5 g BF-200 ALA 10%)a, b | • No indication for erythema, eschar formation or edema during the test or 14 observation period<br>• Slightly yellowish discoloration of the treated skin up to 7 days post dosing (cause: residues of the test substance which could be removed by tepid water).<br>• Clinical signs:<br>Soft stool in 4/5 animals and reduced intake of food in 1/5 animals; most likely indicative of the application stress with fixation (on day 1) or incidental (1 finding in 1F on day 9). Findings are not regarded as test substance related. | T7076581 (ALA-AKPT001) |
| CRL:KBL(NZW)BR rabbits (GLP) | 5F Topical | -4 h | 80 mg ALA HCl/cm² (0.5 g BF-200 ALA 10%) | No edema, very slight erythema/eschar formation (grade 1) in 1 animal at 24 and 48 h post dose.<br>Slightly yellowish discoloration of the 5-ALA-treated skin to 7 days post dosing (cause: residues of the test substance which could be removed by water).<br>• Clinical signs:<br>Soft faeces in 5/5 animals, reduced intake of food in 2/5 animals and water in 1/5 animals up to the end of the study (day 2 - day 7); most likely due to the stress of handling and not drug-related. | T2077909 (ALA-AKPT012) |

| | | | | | |
|---|---|---|---|---|---|
| Himalayan Rabbits (GLP) | 3M Topical (Conjunctival Sac of the right eye) | 24 h | 0.1 mL (100 µg BF-200 ALA 10% ; 10 mg ALA HCl) | • No findings | 25849 (ALAAK-PT027) |
| Hsd Win:NMRI Mice (GLP) | 6F Topical | 3 days | 50 µg/animal (0.5; 1.5, and 5 mg ALA/HCl in 1%, 3%, and 10% BF-200 ALA gela | • No significant increase (>1.4) in lymph node indices.<br>• Significant increase in ear swelling index after application of 3% gel: 1.15, 10% 1.15, and 10% (dark): 1.11 (significant if values are >1.1)<br>• Significant increase in ear weight after application of 3% gel: 1.19, 10% gel: 1.27, and 10% gel (dark): 1.18.) (significant if values are >1.1)<br>• Indication of a non-specific (irritating) immunostimulating potential of the test substance at the mid and high dose. Avoiding light exposure does not reduce the irritant potential significantly. | T8077338/T7077346 (ALA-AKPT007) |
| Hsd Win:NMRI Mice (GLP) | 6F Topical | 3 days | 50 µg/animal (5 mg ALA/HCl in BF-200 ALA 10%gel ) | • Significant increase in the weights of the draining lymph nodes (1.72) and in the stimulation index for cell counts (1.83) compared to control animals after application of the test substance (significant if index >1.4).<br>• Significant increase in ear swelling (1.39) and ear weight (1.40). (Indication of acute response if values are >1.1.)<br>• Calculation of the differentiation index revealed DI <1 (eg 0.53) pointing to an irritating rather than sensitizing potential. | T9077393 (ALA-AKPT013) |

### *Other toxicity studies*

In Ameluz 10% gel three major impurities have been characterized. Specific studies have been conducted to evaluate the local tolerance and sensitization of Ameluz i.e. a patch test performed in rabbits and a local lymph node assay in mice and have been found to demonstrate no sensitization potential with minimal irritation potential observed to be slightly increased by stressed sample.

## 2.3.5. Ecotoxicity/environmental risk assessment

ALA is readily soluble in water and therefore not a potential PBT.

The $PEC_{surfacewater}$ was calculated according to the guideline EMEA/CHMP/SWP/4447/00 and the Q&A EMA/CHMP/SWP/44609/2010.

Taking into account the frequency of administration (twice/year according to the SPC), the calculation of $PEC_{surfacewater}$ gives a value of:

PEC default (1μg/L) * 2/365 days= 0.005 μg/L which is below the action limit of 0.01 μg/L

In addition, as ALA is a product of normal metabolism ubiquitously found in living organisms, the exposure to the environment following administration to patients is not expected to alter significantly the presence of this substance in the environment.

## 2.3.6. Discussion and conclusion on the non-clinical aspects

The applicant has provided an overview of the literature with respect to the mechanism of action of ALA, evidence of potential efficacy as well as known pharmacological aspects associated with ALA-PTD treatment. The therapeutic principle is established and no further pharmacodynamic studies are required in light of the long –term clinical experience with PDT in combination with the topical application of ALA and its use in the treatment of AK. The development of Ameluz, a nanoemulsion-based gel is considered to improve penetration of ALA into the skin and thereby increase efficacy as well as improving the stability.

No relevant secondary systemic pharmacological effects are expected to occur following topical application due to the negligible systemic absorption observed in humans. An aspect of secondary pharmacology that appears relevant is local pain. PDT pain may reflect long-term damage to the skin and the origin of the pain sensation was investigated. Examinations suggest the secretion of substances irritates sensory nerve endings in the neighbourhood of keratinocytes. Investigation of PDT-induced pain was studied in two experiments designed to examine the reaction to PDT of the two cell types involved in pain generation in the skin, namely keratinocytes and peripheral nerve endings. Based that there is evidence to support mechanisms leading to PDT-related pain based on both indirect (via the release of ATP) and direct (activation of peripheral neurons). Both phenomena are considered to be short term effects. The conditions under which the study to investigate direct effects on neurons differed from that of other cell types and was not performed with Ameluz improved penetrance and uptake enhancer. It is unclear if Ameluz applied locally may result in excessive activation of neurons with adverse effects; however no adverse effects other than pain have been reported clinically.

There are considered to be no concerns regarding systemic safety pharmacology effects.

No pharmacodynamic drug interactions studies have been performed. Based on the negligible systemic exposure following Ameluz treatment, no potential drug interaction studies are considered to be required.

The cellular uptake of ALA was investigated i*n vitro* in cultivated keratinocytes or keratinocyte cell lines by measuring PpIX fluorescence. It was shown that the cell penetration of ALA is enhanced in the presence of the nanoemulsion, and a time restricted influence on membrane permeability was identified.

Ex-vivo studies demonstrated a good ALA/PpIX penetration down to the basal membrane of the epidermis within 12 h of incubation was demonstrated in pig skin explants with Ameluz 10% gel. Ameluz 10% gel displayed superior penetration compared to Metvix in terms of PpIX fluorescence intensity and penetration depth at all time points tested. Human explants were studied and reviewed however it is indicated that absorption was found to be low, with minimal potential systemic exposure.

Based on the negligible systemic exposure no new metabolism or elimination studies have been performed. It is considered that the metabolism and elimination of ALA is well know and understood within the literature.

The systemic effects of ALA are considered to be well known within the literature. Based on the clinical observations there is considered to be limited potential for an increase systemic exposure to ALA above endogenous levels via the new formulation.

A 4-time administration of Ameluz 10% with 1-month interval demonstrated the expected adverse effects (erythema, eschar) which are mostly of mild to moderate intensities in Ameluz treated sites. The symptoms were more pronounced in PDT treated areas. No aggravation of symptoms was observed, and the healing process was more rapid from the second application onwards. Histopathological evaluation confirmed a rapid healing process. No obvious differences were noted 28 days after the last treatment when compared to placebo treated skin. The illumination of the skin appeared to be painful; however, a veterinary intervention was not considered to be necessary. No systemic toxicity was observed.

In conjunction with this, several local tolerance studies were performed in mice, rabbits and mini pigs with or without PDT and these studies revealed some skin irritation potential in both the light and dark which was more pronounced following illumination but was observed to be reversible. No sensitization potential was noted and there were no observed ocular irritation effects.

Topical therapy with Ameluz 10% is limited to a single application of the gel to lesional skin and ALA-PDT is an established treatment for AK. Therefore, the lack of carcinogenicity studies is considered to be acceptable.

No studies were conducted by the applicant on the mutagenic and clastogenic potential of ALA or PpIX as part of the development program for Ameluz. Based on published data, the likelihood of sustained genetic damage in surviving cells after ALA-PDT is considered to be low (Fuchs et al., 2000).

ALA has shown no impact on fertility or early embryonic development in mice, however due to the negligible systemic absorption above endogenous levels it is considered that there is limited potential for reproductive effects either on fertility or exposure to the foetus either directly during development or post-natal via the milk.

All impurities have been toxicologically qualified up to the respective specification limit.

Non-clinical data reveal no special hazard for humans based on dermal toxicity studies or studies reported in the literature of repeated dose toxicity, genotoxicity and reproductive toxicity.

The use of 5-aminolaevulinic acid is not expected to pose a risk to the environment.

## 2.4 *Clinical aspects*

## 2.4.1 Introduction

The clinical documentation submitted in support of this application comprises data from one dose-finding study (ALA-AK-CT001) and two confirmatory studies in AK (ALA-AK-CT002 and ALA-AK-CT003).

### *GCP*

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Moreover, the applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

## 2.4.2 Pharmacokinetics

Due to the topical administration of Ameluz 10% gel and the negligible systemic exposure, no studies were performed regarding distribution and binding with plasma proteins, metabolism, comparative PK in healthy subjects and patients, PK related to intrinsic or extrinsic factors, time dependent changes in pharmacokinetics, stereochemistry issues or clinically relevant PK interactions with other medicinal products or substances. Pharmacokinetic data with Ameluz nanoemulsion gel were collected in the dose-ranging study ALA-AK-CT001.

### *Absorption*

ALA is rapidly absorbed after oral administration. Terminal half-lives after oral, intravenous or intravesical administration are short and similar. The non-renal clearance of ALA occurs mainly due to hepatic metabolism. Hepatic first-pass metabolism is not the major factor limiting the oral bioavailability of ALA, but rather gastrointestinal conversion of ALA to PpIX (Dalton et al., 2002).

PpIX concentrations after intravenous administration of ALA were not significantly higher than those observed after oral administration, despite the fact that only 60% of the oral dose of ALA was absorbed. This suggests that the short MRT of ALA in the systemic circulation after intravenous and oral administration of 100 mg ALA does not allow for significant conversion to PpIX in the systemic circulation (Dalton et al., 2002).

### *Distribution*

Not investigated for the topical administration of Ameluz 1%, 3% or 10% in clinical studies.

### *Metabolism*

Aminolaevulinic acid dehydratase (ALAD) condenses 2 molecules of 5-ALA to form the monopyrrole porphobilinogen (PBG). PBG deaminase catalyses the polymerization of four molecules of PBG to hydroxymethylbilane. Hydroxymethylbilane is further metabolized to uroporphyrinogen I and III (by uroporphyrinogen cosynthase). Uroporphyrinogen decarboxylase sequentially removes a carboxylic group from the acetic side chains of each of the pyrrole rings to yield coproporphyrinogen. Coproporphyrinogen oxidase removes a carboxyl group from the propionic groups on 2 of the pyrrole rings to yield protoporphyrinogen IX (Peng et al., 1997), (Kappas et al., 1995).

Protoporphyrinogen oxidase forms PpIX by removing 6 hydrogen atoms from protoporphyrinogen IX. Finally, ferrochelatase mediates the insertion of ferrous iron into the porphyrin macrocycle, forming heme. PpIX is the last step before incorporation of ferrous iron and is located in the mitochondrium (Peng et al., 1997).

### *Elimination*

In study ALA-AK-CT001, urine excretion of ALA was determined after drug application. No increase in urinary excretion of ALA was observed after dosing with Ameluz 1%, 3% or 10% gel confirming the low or negligible exposure after topical administration.

After oral and intravenous ALA administration, ALA seems to be excreted renally and porphyrins formed in the liver are excreted via urine and bile and partially reabsorbed enterally (Mustajoki et al., 1992; O'Flaherty et al., 1980). Saturable renal tubular re-absorption occurs (O'Flaherty et al., 1980). The ALA re-absorption mechanism in man is therefore capable of handling normal to moderately elevated filtered plasma ALA loads.

### *Dose proportionality and time dependency*

Not investigated.

### *Special populations*

In chronic renal failure, serum ALA was elevated to a maximum of three to four times the normal amounts, but its urinary excretion was reduced. The clearance of ALA was on average approximately 12% lower than that of creatinine. In measurement of circadian values in normal subjects, plasma concentrations of ALA appeared reasonably constant (Gorchein et al., 1987).

### *Pharmacokinetic interaction studies*

No studies were submitted. It is, however, possible that concomitant use of medication with known phototoxic or photoallergic potential such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines may enhance the phototoxic reaction to PDT. This is reflected in section 4.5 on the SmPC.

### *Pharmacokinetics using human biomaterials*

No studies were submitted.

## 2.4.3 Pharmacodynamics

Proof-of-concept studies were not conducted by the applicant, since ALA is approved for photodynamic therapy of AK. A literature review has been performed by the applicant.

### *Mechanism of action*

No clinical pharmacodynamic studies have been submitted.

## 2.4.4 Discussion and conclusions on clinical pharmacology

Study ALA-AK-CT001 provides the only pharmacokinetic in vivo data after application of the new nano-emulsion. Systemic exposure is considered irrelevant which is in line with published data and confirmed by in vitro penetration experiments. Therefore, it is reasonable to waive further in depth pharmacokinetic investigations.

Ameluz does not increase 5-aminolaevulinic acid or protoprophyrin IX plasma levels following topical application.

No interaction studies have been performed.

## *2.5 Clinical efficacy*

The applicant conducted one dose-finding and two confirmatory studies in AK encompassing a total of 798 patients and 357 patients (2114 lesions) exposed to Ameluz 10%. The summary of efficacy studies conducted by the applicant is presented in table 3.

**Table 3. Summary of efficacy studies**

| Study ID (centers/ locations) | Study objectives | Study Design | Dosing Regimen | Treatment Duration | No. of subjects | Diagnosis incl. criteria | Primary endpoint |
|---|---|---|---|---|---|---|---|
| ALA-AK-CT001<br><br>(Germany: 11) | dose-finding, safety, tolera-bility | rando-mized, double-blind, placebo-controlled, parallel-group | single-dose appli-cation of 1, 3, 10% ALA HCl and placebo for 3 h | 1 PDT, no re-treat-ment | 1% gel: 25 r<br>3% gel: 25 r<br>10% gel: 28 r<br>Placebo: 27 r | AK, 3-10 lesions on face and/or scalp, diameter 0.5-1.5 cm, minimal distance 1.5 cm | Total lesion clearance 12 weeks after PDT |
| ALA-AK-CT002<br><br>(Ger-many: 23, Austria: 2, Switzer-land: 1) | efficacy, safety | rando-mized, observer-blind, active-compa-rator-controlled, placebo-controlled, parallel-group (3:3:1 ratio) | single-dose appli-cation of 10% ALA HCl, Metvix and placebo for 3 h | 1 PDT, Re-treatment 12 weeks after 1st PDT for not or partially responding lesions | 10% gel: 248 r 248 SP 248 ITT 238 PPS<br>Metvix: 247 r 246 SP 246 ITT 236 PPS<br>Placebo: 76 r 76 SP 76 ITT 65 PPS | Mild to moderate AK (Olsen I-II), 4-8 lesions on face and/or scalp, diameter 0.5-1.5 cm, minimal distance 1.0 cm | Subjects with total lesion clearance 12 weeks after last PDT |
| ALA-AK-CT003<br><br>(Germany: 8) | efficacy, safety | rando-mized, double-blind, placebo-controlled, parallel-group (2:1 ratio) | single-dose appli-cation of 10% ALA HCl and placebo for 3 h | 1 PDT, Re-treatment 12 weeks after 1st PDT for not or partially responding lesions | 10% gel: 81 r 81 SP 80 FAS 77 PPS<br>Placebo: 41 r 41 SP 40 FAS 37 PPS | Mild to moderate AK (Olsen I-II), 4-8 lesions on face and/or scalp, diameter 0.5-1.5 cm, minimal distance 1.0 cm | Subjects with total lesion clearance 12 weeks after last PDT |

## 2.5.1 Dose response study

- **Study ALA-AK-CT001**

A placebo-controlled, randomized, 4-armed study was performed to determine an effective, safe and tolerable dose of Ameluz gel for the treatment of AK.

In total 105 patients were treated with either Ameluz 1%, 3% or 10% or placebo, 104 patients completed the study, one patient dropped out prior to the week 8 assessment due to a planned surgery.

Two illumination devices with a broad light spectrum were applied in this study (Hydrosun/PhotoDyn 505 and Waldmann PDT1200L). With the low number of subjects irradiated with a Waldmann PDT 1200L (overall 10.5% of the subjects), similar clearance rates were observed for both devices.

The total clearance rate of AK lesions, defined as the percentage of baseline lesion count within the target treatment areas showing complete remission at week 12 post treatment was defined as primary endpoint.

The main secondary endpoint was the reduction in AK lesion area per subject. Additional secondary endpoints included the number of totally cleared subjects, the safety and the cosmetic outcome.

The table below gives an overview of the main treatment characteristics and the efficacy results.

**Table 4: Baseline characteristics and efficacy rates of phase II study ALA-AK-CT001 (FAS population)**

| Variable | BF-200 ALA 1%, N=25 | BF-200 ALA 3%, N=25 | BF-200 ALA 10%, N=28 | Placebo N=27 |
|---|---|---|---|---|
| Number of lesions, n | 128 | 134 | 147 | 135 |
| Size, $mm^2$ (mean ± SD) | | | | |
| Overall | 62.6 ± 41.9 | 70.7 ± 51.2 | 62.1 ± 44.6 | 57.3 ± 40.3 |
| Face and forehead | 64.8 ± 40.9 | 73.3 ± 50.6 | 69.2 ± 47.6 | 55.5 ± 40.9 |
| Bald scalp | 56.8 ± 44.5 | 67.4 ± 52.1 | 52.6 ± 38.6 | 59.7 ± 39.8 |
| Severity grade, n (%) | | | | |
| Mild | 41 (32.0) | 71 (53.0) | 70 (47.6) | 51 (37.8) |
| Moderate | 83 (64.8) | 62 (46.3) | 76 (51.7) | 74 (54.8) |
| Severe | 4 (3.1) | 1 (0.7) | 1 (0.7) | 10 (7.4) |
| | | | | |
| Efficacy (12 weeks after PDT) | | | | |
| Total lesion clearance. n (%) | 35/128 (27.3) | 29/134 (21.6) | 79/144 (54.9) [a] | 28/135 (20.7) |
| Lesion size, $mm^2$ (mean ± SD) (% reduction) | | | | |
| Face and forehead | 18.8 ± 21.9 (71) | 26.1 ± 33.2 (64) | 16.8 ± 26.4 (76) | 32.2 ± 43.2 (42) |
| Bald scalp | 45.2 ± 40.6 (20) | 29.7 ± 35.3 (56) | 16.9 ± 29.6 (68) | 39.1 ± 39.4 (35) |
| Total patient clearance N(%) | 1 ( 4.0) | 4 (16.0) | 7 (25.9) | 1 ( 3.7) |

a: *P*<0.0001 (chi-square test, and CMH) to Placebo

Only for the Ameluz 10% treated patients a significant difference to placebo was achieved with respect to the primary endpoint. At week 12 after treatment 54.9% of the lesions showed complete remission for 10% ALA (50.6% of the lesions on the face and forehead and 60.3% of the lesions on the bald scalp). Lower clearance rates were observed for placebo (20.7%), 1% ALA (27.3%) and 3% ALA (21.6%). Statistically significant differences between Ameluz 10% to the other treatment groups were also seen regarding the subgroups of patients >68 years, patients with skin type III and lesions of moderate intensity.

Concerning secondary endpoints, Ameluz 10% gel showed the highest total patient clearance, and the largest reduction in lesion number and lesion size in face and forehead (50% and 76%, respectively) and bald scalp (60.4% and 68%, respectively) compared to the other treatments 12 weeks after PDT.

## 2.5.2 Main studies

- **Study ALA-AK-CT002**

This was a randomised, observer-blind, multinational, controlled parallel-group (3:3:1 ratio) phase III study to evaluate the efficacy and safety of a nanoemulsion gel formulation Ameluz, in comparison with Metvix and placebo, for the treatment of actinic keratosis with photodynamic therapy.

## *Methods*

### *Study Participants*

Main inclusion criteria were male and female subjects between 18 and 85 years of age, diagnosed to have at least 4 but not more than 8 lesions of mild to moderate AK (Olsen grade I or II) in their face and / or on the bald scalp, confirmed by a pre-study biopsy.

The scale described by Olsen et al.,1991 is the following:

| **Grade** | | **Clinical description of intensity grading** |
|---|---|---|
| 0 | none | no AK lesion present, neither visible nor palpable |
| I | mild | flat, pink maculae without signs of hyperkeratosis and erythema, slight palpability, with AK felt better than seen |
| II | moderate | pink to reddish papules and erythematous plaques with hyperkeratotic surface, moderately thick AK that are easily seen and felt |
| III | severe | very thick and / or obvious AK |

The diameter of each AK lesion was to be not less than 0.5 cm and not greater than 1.5 cm. Adjacent AK lesions had to show a distance of more than 1.0 cm to one another.

The following main criteria excluded subjects from study participation: known hypersensitivity to ALA, current immunosuppressive therapy, porphyria, hypersensitivity to porphyrins, photodermatoses, inherited or acquired coagulation defects, clinically significant/unstable medical conditions, other malignant or benign tumours of the skin within the treatment area, women of child-bearing potential without reliable contraception, and pregnant or breast-feeding women.

### *Treatments*

For each subject, one of three formulations (Ameluz 10%, placebo (the nanoemulsion gel vehicle without the active ingredient ALA), and the marketed product Metvix (a cream containing 16% methyl-aminolevulinate)) was applied to the target AK lesions.

After thorough preparation of the lesions, including removal of all scabs, crusts and hyperkeratotic parts by curettage, the skin sites were to be cleaned with alcohol (ethanol or isopropanol. 1 tube containing 2 g of test drug was dispensed for 1 PDT session, enough to cover up to 8 distinct AK lesions with a maximum diameter of 1.5 cm.

The gel was allowed to dry for approximately 10 min. Thereafter, an occlusive, light-tight dressing was placed over the lesions. After the incubation time of 3 h ± 10 min, the occlusion was removed and the remnant gel wiped off with a 0.9% saline solution immediately before illumination of the target area with a suitable red light source for 8 to 15 min depending on the device used.

Subjects with non-responding AK lesions were re-treated with the same medication after 12 weeks.

### *Objectives*

The primary objective of the study was to compare the efficacy of a nanoemulsion gel formulation containing 10% 5-aminolaevulinic acid hydrochloride (5-ALA) as active ingredient (also referred to as

Ameluz) with the marketed product Metvix and with placebo, for the treatment of AK with PDT. Secondary objective was to evaluate the safety and secondary efficacy parameters related to Ameluz gel for treatment of AK with PDT.

### *Outcomes/endpoints*

The primary efficacy analysis variable was the overall subject complete response rate assessed 12 weeks after the last PDT. A subject was classified as an overall complete responder if all treated lesions were cleared after either PDT1 or PDT2, if re-treated. A missing 12-week assessment was imputed by the preceding 4-week assessment using a LOCF approach. In case no assessment was available at all, the subject was regarded as a non-responder.

The main secondary efficacy endpoints were the subject complete response (complete clearance of all treated lesions) at each assessment, the subject partial response (complete clearance of at least 75% of the treated lesions) at each assessment the lesion complete response (completely cleared individual lesions) at each assessment and the overall cosmetic outcome 12 weeks after the last PDT.

### *Sample size*

To establish non-inferiority of BF-200 ALA 10% to Metvix, the one-side lower 97.5% confidence interval for the difference in overall subject complete response rate assessed 12 weeks after the last PDT was compared to the pre-specified non-inferiority margin of –15%. The sample size of 210 subjects per treatment arm has a power of at least 90% to establish non-inferiority of Ameluz 10% to Metvix using a non-inferiority margin of –15% and assuming response rates of 70% for both Ameluz 10% and Metvix. Assuming a dropout rate of 20%, 264 subjects per active treatment group needed to be randomized in order to achieve 210 evaluable subjects per treatment group in the PP population.

To establish superiority of Ameluz 10% over placebo, a sample size of 264:88 subjects (Ameluz:placebo) has a power of more than 90%, even if very conservative response rates of 65% for the Ameluz UZ group and 40% for placebo are assumed using a chi-square test with continuity correction and a two-sided significance level of 0.05.

### *Randomisation*

The randomization schedule linked sequential numbers to treatment codes allocated at random with a 3:3:1 randomization ratio.

### *Blinding (masking)*

The study was an observer-blinded study design.

### *Statistical methods*

Two primary hypotheses were tested using a hierarchical testing procedure as follows:

The first primary null hypothesis was that the overall complete responder rate assessed 12 weeks after the last PDT for subjects treated with Ameluz was equal to that of subjects treated with placebo.

The superiority of Ameluz over placebo was tested using a chi-square test with a 2-sided significance level of 0.05. Superiority of Ameluz over placebo was established if the first primary null hypothesis could be rejected.

•The second primary null hypothesis was that the overall subject complete responder rate assessed 12 weeks after the last PDT for subjects treated with Ameluz was inferior compared to the corresponding responder rate for subjects treated with Metvix as specified by a non-inferiority margin of Δ=15%.

The difference in response rates, together with a 1-sided lower 97.5% CI, was calculated to assess non-inferiority. Non-inferiority of Ameluz in comparison to Metvix was established if the second primary null hypothesis could be rejected.

Following the hierarchical testing strategy, the second primary null hypothesis was only planned to be tested if the first primary null hypothesis was rejected.

Both primary hypotheses were to be tested 2-sided at a significance level of 0.05.

The hierarchical testing procedure controls for type I error inflation due to multiple testing. Therefore, no adjustment of the significance level was necessary. The first primary analysis was performed on the ITT population and the second primary analysis on the PP population.

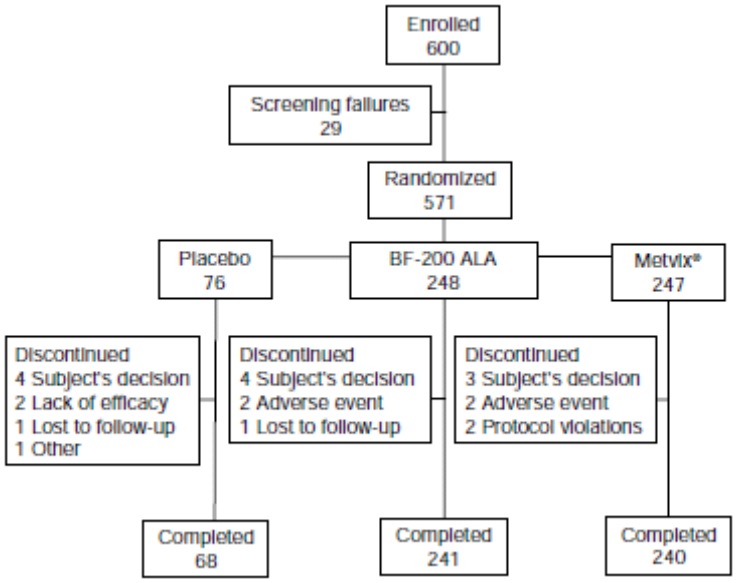
No interim analysis was performed.

## *Results*

## *Participant flow*

The patient disposition is presented in Figure 4.

**Figure 4. Patient disposition, study ALA-AK-CT002**




## *Recruitment*

The trial was initiated 8-April-2008 (first informed consent signed) and finalised in 21-August-2009 (last subject completed clinical part of study).

## *Conduct of the study*

The original protocol was amended twice.

The first amendment, dated Jan 17th, 2008 concerned the addition of a second, optional biopsy of AK lesions at the end of the clinical part of the study.

The second amendment, dated Aug 20th, 2008 incorporated changes concerning the handling of new lesions in the treatment area after the first PDT and the definition of concomitant medication.

### *Baseline data*

Baseline demographic characteristics and disease characteristics of the patients are presented in the table 5.

**Table 5: Baseline demographic characteristics and disease characteristics at baseline (ITT population)**

| Population | | No. (%) subjects | | | |
|---|---|---|---|---|---|
| | | Placebo (N=76) | BF-200 ALA (N=248) | Metvix® (N=246) | Total (N=570) |
| Age (years) | Mean ± SD | 71.5 ± 6.68 | 70.2 ± 7.18 | 71.0 ± 6.93 | 70.7 ± 7.01 |
| | Range | 51 - 84 | 39 - 87 | 44 - 85 | 39 - 87 |
| Gender, n (%) | Male | 60 (78.9) | 214 (86.3) | 205 (83.3) | 479 (84.0) |
| | Female | 16 (21.1) | 34 (13.7) | 41 (16.7) | 91 (16.0) |
| Height (cm) | | | | | |
| Male | Mean ± SD | 177.4 ± 6.63 | 175.5 ± 6.45 | 174.9 ± 6.55 | 175.5 ± 6.55 |
| | Range | 155 - 189 | 158 - 190 | 152 - 193 | 152 - 193 |
| Female | Mean ± SD | 161.8 ± 5.08 | 162.1 ± 6.78 | 162.7 ± 5.57 | 162.3 ± 5.92 |
| | Range | 152 - 170 | 148 - 179 | 151 - 175 | 148 - 179 |
| Weight (kg) | | | | | |
| Male | Mean ± SD | 85.5 ± 10.04 | 81.9 ± 10.55 | 81.1 ± 10.10 | 82.0 ± 10.37 |
| | Range | 64 - 115 | 56 - 130 | 54 - 122 | 54 - 130 |
| Female | Mean ± SD | 68.5 ± 10.88 | 69.7 ± 8.82 | 71.6 ± 10.62 | 70.3 ± 9.99 |
| | Range | 51 - 85 | 52 - 90 | 51 - 98 | 51 - 98 |
| BMI (kg/m²) | Mean ± SD | 27.0 ± 2.99 | 26.6 ± 3.16 | 26.6 ± 3.22 | 26.6 ± 3.16 |
| | Range | 21 - 35 | 19 - 41 | 19 - 40 | 19 - 41 |
| Family history of skin cancer, n (%) | | | | | |
| No family history | | 71 (93.4) | 234 (94.4) | 231 (93.9) | 536 (94.0) |
| Basal cell carcinoma | | 4 (5.3) | 8 (3.2) | 3 (1.2) | 15 (2.6) |
| Skin cancer (not specified) | | 0 | 1 (0.4) | 4 (1.6) | 5 (0.9) |
| Melanoma | | 0 | 4 (1.6) | 4 (1.6) | 8 (1.4) |
| Other | | 1 (1.3) | 2 (0.8) | 4 (1.6) | 7 (1.2) |
| Fitzpatrick skin typing, n (%) | | | | | |
| I (0-7) | | 2 (2.6) | 3 (1.2) | 6 (2.4) | 11 (1.9) |
| II (8-16) | | 27 (35.5) | 90 (36.3) | 82 (33.3) | 199 (34.9) |
| III (17-24) | | 43 (56.6) | 118 (47.6) | 133 (54.1) | 294 (51.6) |
| IV (25-30) | | 4 (5.3) | 35 (14.1) | 23 (9.3) | 62 (10.9) |
| V to VI (>30) | | 0 | 2 (0.8) | 2 (0.8) | 4 (0.7) |

## Numbers analysed

The number of subjects in each of the study populations is given by treatment group in Table 6.

**Table 6. Number of subjects in the patient populations**

| Population | No. (%) subjects | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | BF-200 ALA | | Metvix® | | Total | |
| Enrolled | | | | | | | 600 | |
| Randomized | 76 | (100) | 248 | (100) | 247 | (100) | 571 | (100) |
| ITT population | 76 | (100) | 248 | (100) | 246 | (99.6) | 570 | (99.8) |
| Safety population | 76 | (100) | 248 | (100) | 246 | (99.6) | 570 | (99.8) |
| PP population | 65 | (85.5) | 238 | (96.0) | 236 | (95.5) | 539 | (94.4) |

## Outcomes and estimation

**Primary endpoint**

The results of the primary endpoint are presented in table 7.

**Table 7: Study ALA-AK-CT002- Efficacy results Primary endpoint – Subjects with total AK lesion clearance 12 weeks after last PDT**

| Study Analysis population | Number (%) of subjects | | | Difference to BF-200 ALA 10% | |
|---|---|---|---|---|---|
| | Placebo | BF-200 ALA 10% | Metvix | Placebo | Metvix |
| ITT population | 13/76 (17.1%) | 194/248 (78.2%) | 158/246 (64.2%) | 61.1% [95% CI: 51.2; 71.0][a] $P<0.0001$[b] | 14.0% [97.5% CI: 5.9; ∞][c] |
| PP population | 13/65 (20.0%) | 189/238 (79.4%) | 154/236 (65.3%) | 59.4% [95% CI: 48.4; 70.4][a] $P<0.0001$[b] | 14.2% [97.5% CI: 6.0; ∞][c] |

a 2-sided
b $\chi 2$ test
c 1-sided

**Main secondary efficacy endpoint**

The total AK lesion clearance with BF-200 ALA was 90.4% vs 37.1% with placebo and 83.2% with Metvix (Table 8).

**Table 8: Study ALA-AK-CT002-Efficacy results-Main secondary endpoint – Total AK lesion clearance 12 weeks after last PDT**

| Study Population | Number (%) of lesions | | | Difference to BF-200 ALA 10% | |
|---|---|---|---|---|---|
| | Placebo | BF-200 ALA 10% | Metvix | Placebo | Metvix |
| ITT population | 182/490 (37.1%) | 1359/1504 (90.4%) | 1295/1557 (83.2%) | 53.2% | 7.2% |

**Other secondary efficacy endpoints**

- *Subject complete response (complete clearance of all treated lesions) at each assessment*

Ameluz 10% was superior to placebo in total AK lesion clearance per subject at each assessment. Differences vs placebo ranged between 32.0 and 61.1% (ITT analysis) and between 31.8 and 59.4% (PP analysis); all differences were statistically significant ($P<0.0001$) in secondary analyses.

Differences between Ameluz 10% and Metvix ranged between 4.6 and 14.6% (ITT analysis) and between 4.8 and 15.3% (PP analysis) in favour of Ameluz 10%.

- *Subject partial response (complete clearance of at least 75% of the treated AK lesions) at each Assessment*

Ameluz 10% was superior to placebo in clearing at least 75% of AK lesions at each assessment. Differences vs placebo ranged between 45.7 and 60.8% (ITT analysis) and between 45.8 and 58.6% (PP analysis); all differences were statistically significant ($P$<0.0001) in secondary analyses.

Differences between Ameluz 10% and Metvix ranged between 4.1 and 14.2% (ITT analysis) and between 4.2 and 14.8% (PP analysis) in favour of Ameluz 10%.

- *Reduction in total AK lesion area per subject at each assessment*

Ameluz 10% was superior to placebo in reducing total AK lesion area at each assessment. Differences vs placebo ranged between 42.2 and 52.0% (ITT analysis); all differences were statistically significant ($P$<0.0001) in secondary analyses.

Differences between Ameluz 10% and Metvix ranged between 2.8 and 4.5% (ITT analysis); all differences except 3-4 weeks after PDT2 were statistically significant (between $P$=0.04 and 0.0007) in secondary analyses.

- *Overall cosmetic outcome 12 weeks after the last PDT*

"Very good" or "good" cosmetic outcomes 12 weeks after last PDT were more frequent with Ameluz 10% (43.1%) than with placebo (36.4%) and similar to Metvix (45.2%). ''Unsatisfactory'' or ''impaired'' cosmetic outcome observed in 7.9%, 8.1 % and 18.2 % of subjects in Ameluz, Metvix and placebo group respectively.

- *Skin quality assessment*

Improvements in skin quality from baseline to 12 weeks after the last PDT occurred in all 3 treatment groups; with subjects experiencing most improvements in "roughness, dryness, scaling" (improvement in 40.0% subjects with Ameluz 10%, 46.4% with Metvix and 27.3% with placebo). Regarding hyperpigmentation (independent of texture change or hypopigmentation) and atrophy values improved from baseline 13.6 and 27.3% with placebo, 22.8 and 38.2% with Ameluz and 29.5 and 34.6% with Metvix.

**Recurrence rates at Follow-up for study ALA-AK-CT002**

Patients who completed ALA-AK-CT002 study were followed up at for two additional visits scheduled 6 ± 0.5 months after last PDT and 12 ± 1 month after the last PDT in order to evaluate recurrent AK lesions developing within the treatment area since the end of the study visit.

549 subjects completed the clinical study part of whom 78.2% showed complete clearance in the Ameluz 10% group and 64.2% and 17. 1% in the Metvix and placebo groups, respectively. 92.6% of the patients completed the 12 months follow-up phase: 84.2% in the placebo group, 94% in the Ameluz 10% group and 93.9% in the Metvix group.

Recurrence rates after 12 months were 41.6% for Ameluz (95% CI: 34.4-49.1) and 44.8% for MAL (95% CI: 36.8-53.0) and were dependent on the light spectrum used for illumination, in favour of narrow spectrum lamps. Prior to the decision to undergo photodynamic therapy it should be taken into consideration that the probability of a subject to be completely cleared 12 months after the last treatment was 53.1% or 47.2% for treatment with Ameluz and 40.8% or 36.3% for MAL treatment with narrow spectrum lamps or all lamp types, respectively. The probability of patients in the Ameluz group to require only 1 treatment and remain completely cleared 12 months after the photodynamic therapy was 32.3%, that of patients in the MAL group 22.4% on average with all lamps.

- **Study ALA-AK-CT003**

This was a randomised, double-blind, inter-individual, two-armed phase III multi-centre study evaluating the safety and efficacy of Ameluz versus placebo in the treatment of actinic keratosis when using PDT.

### *Methods*

### *Study Participants*

Main inclusion criteria were male and female subjects between 18 and 85 years of age, diagnosed to have at least 4 but not more than 8 lesions of mild to moderate AK (Olsen grade I or II) in their face or on the bald scalp, confirmed by a pre-study biopsy. The diameter of each AK lesion was to be not less than 0.5 cm and not greater than 1.5 cm. Adjacent AK lesions had to show a distance of more than 1.0 cm to one another.

The following main criteria excluded subjects from study participation: known hypersensitivity to ALA, current immunosuppressive therapy, porphyria, hypersensitivity to porphyrins, photodermatoses, inherited or acquired coagulation defects, clinically significant/unstable medical conditions, other malignant or benign tumours of the skin within the treatment area, women of child-bearing potential without reliable contraception, and pregnant or breast-feeding women.

## Treatments

For each subject, one of two formulations (Ameluz 10% or placebo (the nanoemulsion gel vehicle without the active ingredient ALA), was applied to the target AK lesions.

Scabs, crusts, or hyperkeratosis were thoroughly removed from the AK lesions. In addition, all lesion surfaces were abraded using a curette or scalpel blade avoiding bleeding and were cleaned with an ethanol-soaked cotton pad prior to drug application and incubation. 1 tube containing 2 g of test drug was dispensed for 1 PDT session, enough to cover up to 8 distinct AK lesions with a maximum diameter of 1.5 cm.

After application, the gel was allowed to dry for approximately 10 min. Thereafter, an occlusive, light-tight dressing was placed over the lesions. After the incubation time of 3 h ± 10 min, the occlusion was removed and the remnant gel wiped off with a 0.9% saline solution immediately before illumination of the target area with a suitable red light source for 11 to 15 min.

### *Objectives*

The objectives of the study were to assess the efficacy, safety, tolerability and cosmetic outcome of topical PDT with a new nanoemulsion formulation of 5-aminolaevulinic acid hydrochloride (Ameluz) in the treatment of AK.

### *Outcomes/endpoints*

The primary efficacy endpoint was the total AK clearance rate, defined as the number of subjects with complete remission of all AK lesions in the target area(s) assessed 12 weeks after the last PDT.

The main secondary efficacy endpoints were the subject complete response (complete clearance of all treated lesions) at each assessment, the subject partial response (complete clearance of at least 75% of the treated lesions) at each assessment, the lesion complete response (completely cleared individual lesions) at each assessment and the overall cosmetic outcome 12 weeks post-treatment.

### *Sample size*

Based on the phase IIb study ALA-AK-CT001 the applicant assumed clearance rates of 35% (active) and 10% (placebo), respectively, a total number of 67 (active) and 34 (placebo) subjects would suffice for 80% power to show statistically significant superiority over placebo with a one-sided type I error of 2.5% . Accounting for possible drop-outs, a total of 120 subjects were to be included in this study.

### *Randomisation*

The patients were randomly assigned to receive Ameluz or placebo in a 2:1 ratio.

### *Blinding (masking)*

The study was double blinded.

### *Statistical methods*

The primary endpoint (clearance rate) was estimated as a relative frequency separately for BF- 200 ALA and placebo treatments and it was tested if a statistically significant difference in the clearing rates existed between Ameluz and placebo.

A Cochran-Mantel-Haenszel test, accounting for centres as stratifying variable, was used. The test was evaluated as two-sided test at an alpha-level of 0.05, but superiority of active treatment over placebo could only be concluded if, besides statistical significance, the clearance for the active treatment was higher than for the placebo treatment.

This evaluation corresponds to a one-sided test of superiority evaluated at $\alpha=0.025$.

Furthermore, 95% CIs according to the method of Pearson-Clopper were calculated for the clearance rates of each of the treatments.

The analysis of the primary endpoint was performed for the FAS population (all subjects who received treatment and had at least one post-dose assessment of the clearance of the AK lesions in the target area of the primary variable) and the PP population (all subjects who had no significant protocol violations and for whom clearance of all lesions present at baseline could be assessed after 12 weeks of treatment). The analysis of the secondary endpoints was performed for the FAS and the PP population.

No interim analysis was performed.

## *Results*

### *Participant flow*

The patient disposition is presented in Figure 5.

**Figure 5. Disposition of subjects**

| | Treatment group | | |
|---|---|---|---|
| | 10% BF-200 ALA n (%) | Placebo n (%) | Overall n (%) |
| Number of subjects treated with first PDT* | 81 | 41 | 122 |
| Number of subjects completing week 12 assessments after the 1st PDT | 80 (98.8%) | 40 (97.6%) | 120 (98.4%) |
| Number of subjects treated with second PDT | 39 (48.1%) | 34 (82.9%) | 73 (59.8%) |
| Number of subjects completing week 12 assessments after the 2nd PDT | 39 (48.1%) | 33 (80.5%) | 72 (59.0%) |
| Number of subjects completing the study | 77 (95.1%) | 37 (90.2%) | 114 (93.4%) |
| Number of subjects withdrawn from the study | 4 (4.9%) | 4 (9.8%) | 8 (6.6%) |
| Reason for withdrawal | n (subject no.) | n (subject no.) | |
| Other: Refused 2nd PDT/ Withdrew consent for 2nd PDT | 3 (004, 064, 065) | 2 (025, 063) | 3 (2.5%) 2 (1.6%) |
| Withdrew consent | | 2 (061*, 068**) | 2 (1.6%) |
| Protocol deviation | 1 (106) | | 1 (0.8%) |

* 2 subjects (one in BF-200 ALA and one in placebo group did not receive an assessment of AK lesions 3 weeks after first PDT and were therefore not included in the FAS population
* after 2nd PDT, ** after 1st PDT due to ineffective treatment

## Recruitment

The trial was initiated 13-December-2007 (first informed consent signed) and finalised in 1-October-2008 (last subject completed clinical part of study).

### *Conduct of the study*

The original protocol was amended once. The amendment (dated November 2nd, 2007) included changes to the criteria for a second PDT (criteria were given in more detail).

### *Baseline data*

Baseline demographics and baseline disease characteristics and prior therapy information are summarised in tables 9 and 10.

**Table 9. Summary of demographic characteristics (FAS population)**

| | | Treatment group | | |
|---|---|---|---|---|
| | | BF-200 ALA N=80 | Placebo N=40 | Overall N=120 |
| Age (years) | Mean (SD) | 70.4 (5.2) | 70.8 (6.7) | 70.5 (5.7) |
| | Range | 58-82 | 57-85 | 57-85 |
| Height (cm) | Mean (SD) | 173.4 (6.8) | 170.6 (8.2) | 172.5 (7.4) |
| | Range | 146-192 | 146-188 | 146-192 |
| Weight (kg) | Mean (SD) | 79.61 (10.54) | 78.28 (13.16) | 79.17 (11.44) |
| | Range | 59.0-105.5 | 55.0-120.0 | 55.0-120.0 |
| BMI (kg/m²) | Mean (SD) | 26.54 (3.77) | 26.96 (4.58) | 26.68 (4.05) |
| | Range | 19.4-42.2 | 19.9-44.6 | 19.4-44.6 |
| Male | N (%) | 72 (90.0%) | 31 (77.5%) | 103 (85.8%) |
| Female | N (%) | 8 (10.0%) | 9 (22.5%) | 17 (14.2%) |

**Table 10. AK lesion numbers and severity grade (according to OLSEN) at baseline (safety population)**

| Lesion variable | Placebo n=41 | BF-200 ALA 10% n=81 | Total n=122 |
|---|---|---|---|
| Total number of lesions at baseline | 225 | 463 | 688 |
| Face | 149 (66.2) | 291 (62.9) | 440 (64.0%) |
| Scalp | 76 (33.8) | 172 (37.1) | 248 (36.0%) |
| Severity grade, n (%) | | | |
| Mild | 127 (56.4%) | 247 (53.3%) | 374 (54.4%) |
| Moderate | 98 (43.6%) | 216 (46.7%) | 314 (45.6%) |
| Severe | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

Abbreviations: ALA=5-amino levulinic acid

## Numbers analysed

The number of subjects in each of the study populations is given by treatment group in table 11.

**Table 11. Study populations**

| | | Treatment group | | |
|---|---|---|---|---|
| | | BF-200 ALA | Placebo | Overall |
| Subjects Treated | N | 81 | 41 | 122 |
| Safety Population | N (%) | 81 (100%) | 41 (100%) | 122 (100%) |
| Full Analysis Set | N (%) | 80 (98.8%) | 40 (97.6%) | 120 (98.4%) |
| Per Protocol Set | N (%) | 77 (95.1%) | 37 (90.2%) | 114 (93.4%) |

## Outcomes and estimation

**Primary endpoint**

The results of the primary endpoint are presented in table 12.

**Table 12. Study ALA-AK-CT003-Efficacy results-Primary endpoint-Subjects with total AK lesion clearance 12 weeks after last PDT**

| Population | No. (%) subjects | | Difference between BF-200 ALA and placebo |
|---|---|---|---|
| | Placebo | BF-200 ALA 10% | |
| FAS population | 5/40 (12.5%) | 53/80 (66.3%) | 53.8% $P<0.0001$[a] |
| PP population | 4/37 (10.8%) | 49/77 (63.6%) | 52.8% $P<0.0001$[a] |

a Cochran-Mantel-Haenszel test

**Main secondary efficacy endpoint**

Total AK lesion clearance with Ameluz 10% was 81.1% vs 20.9% with placebo (FAS population) and 81.3% vs 22.0%, respectively (PP population) (table 13).

**Table 13. Study ALA-AK-CT003-Efficacy results-Main secondary endpoint-Total AK lesion clearance 12 weeks after last PDT**

| Population | No. (%) subjects | | Difference between BF-200 ALA 10% and placebo[a] |
|---|---|---|---|
| | Placebo | BF-200 ALA 10% | |
| FAS population | 46/220 (20.9%) | 369/455 (81.1%) | 60.2% |
| PP population | 45/205 (22.0%) | 353/434 (81.3%) | 59.3% |

[a]95%CI did not overlap between placebo and BF-200 ALA group

**Other secondary efficacy endpoints**

- *Subject complete response (complete clearance of all treated lesions) at each assessment*

Ameluz 10% was superior to placebo in total AK lesion clearance per subject at each assessment. Differences vs placebo ranged between 31.3 and 53.8%; all differences were statistically significant (*P*<0.0001 or 0.0002) in secondary analyses.

- *Subject partial response (complete clearance of at least 75% of the treated AK lesions) at each assessment*

Ameluz 10% was superior to placebo in clearing at least 75% of AK lesions at each assessment. Differences vs placebo ranged between 46.3 and 61.3% (FAS analysis); all differences were statistically significant (*P*<0.0001) in secondary analyses.

- *Reduction in total AK lesion area per subject at each assessment:*

Mean lesion size of the lesions on the face and forehead per subject was reduced from 70.8 mm2 at baseline to 6.3 mm2 at the end of the study in the Ameluz 10% group.

On the bald scalp mean lesion size decreased from 71.3 mm2 to 10.0 mm2.

The corresponding reductions in the placebo group were for face and forehead from 77.3 mm² to 58.4 mm² and for bald scalp from 63.8 mm² to 41.7 mm².

Until the end of the study the mean total lesion area within the target treatment area per subject decreased after treatment with Ameluz by 360.2 mm2 (from 403.8 mm2 to 43.6 mm2) and after treatment with placebo by 110.1 mm2 (from 399.3 mm2 to 289.2 mm2, *P*<0.0001).

- *Overall cosmetic outcome 12 weeks after the last PDT*

"Very good" and "good" cosmetic outcomes were more frequent with Ameluz 10% (47.6%) than with placebo (25.0%). ''Unsatisfactory'' or ''impaired'' outcome has been reported in 3.8 % and 22.5 % of subjects in AMELUZ and placebo group respectively.

- *Skin quality assessment*

Skin quality improved during the course of the study in the Ameluz 10% group, especially for "roughness, dryness, scaling" (improvement in 41.3% subjects with Ameluz 10% and 15.0% with placebo; *P*=0.0123) and "hyperpigmentation" (improvement in 20.1% subjects with Ameluz 10% and 17.5% with placebo; *P*=0.0389).

For all other skin irritation parameters, more than 80% of all subjects showed no changes from baseline to the end of the study.

**Recurrence rates at Follow-up for study ALA-AK-CT003**

Seventy-seven of the Ameluz 10% treated patients were followed up, of whom 53 subjects had shown complete clearance at the end of the study. All subjects comprised 353 cleared lesions which were followed up.

At month 6 after the last PDT, 25 out of 353 cleared lesions (7.1%) in Ameluz 10% treated patients showed a recurrent AK and further 28 lesions (7.9%) were recurrent in month 12, i.e. overall 53 lesions were recurrent at the end of the follow-up period (15.0%). Prior to the decision to undergo photodynamic therapy it should be taken into consideration that the probability of a subject to be completely cleared 12 months after the last treatment was 67.5% or 46.8% for treatment with Ameluz with narrow spectrum lamps or all lamp types, respectively. The probability to require only one treatment with Ameluz and remain completely cleared 12 months later was 34.5% on average with all lamps.

42 subjects (79.2%) who had shown complete clearance 3 months after the last PDT remained without any recurrent AK lesions until month 6, and 34 subjects (64.2%) were still completely cleared at the

end of the 12-month follow-up period. Nine subjects (17.0%) showed at least 1 recurrent lesion in month 6 and further 6 subjects (11.3%) in month 12.

## Ancillary analyses

The efficacy results (ITT and FAS analysis of studies ALA-AK-CT002 and ALA-AK-CT003) were analyzed in subpopulations with regard to the primary efficacy endpoint "subjects with total AK lesion clearance" These included analyses by sex, age, number of AK lesions at baseline, maximum AK baseline severity, AK lesion area, skin type, target areas, lamp type, and illumination source

The overall superior efficacy of Ameluz 10% over placebo observed in the overall subject populations was confirmed in all subpopulations analyzed. In addition, Ameluz 10% had numerically higher AK clearance rates per subject than Metvix in most of the subpopulation analyzed (data not shown).

In addition, the applicant performed sub analyses in studies ALA-AK-CT002 and ALA-AK-CT003 concerning the primary efficacy endpoint stratified by illumination lamps and wavelength spectra.

In study ALA-AK-CT002 the use of illumination sources with a narrow wavelength spectrum resulted in higher proportion of responders with Ameluz or Metvix, but not with placebo, than sources with a broad wavelength spectrum: 84.8% vs 71.5% with Ameluz 10% and 67.5% vs 61.3% with Metvix, but 12.8% vs 21.6% with placebo. In general Ameluz 10% leads to better results than Metvix with any of the illumination sources. An exception is the Waldmann lamp which yielded slightly better results with Metvix compared to Ameluz 10% (92.3% vs 86.7%), but was used in few subjects only (5.4%).

In study ALA-AK-CT003 the use of illumination sources with a narrow wavelength spectrum resulted in higher proportion of responders with placebo or Ameluz than sources with a broad wavelength spectrum: 13.3% vs 12.0% with placebo and 87.1% vs 53.1% with Ameluz 10%.

Irrespective of the illumination source, Ameluz 10% was generally superior to the other two treatments. The overall effects of narrow-spectrum illumination were more pronounced than those observed with broad-spectrum illumination.

## Summary of Main Efficacy Results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 14. Summary of Efficacy for trial ALA-AK-CT002**

| **Title:** A randomized, observer-blind, multinational phase III study to evaluate the efficacy and safety of a nanoemulsion gel formulation BF-200 ALA, in comparison with Metvix and placebo, for the treatment of actinic keratosis with photodynamic therapy. | | |
|---|---|---|
| Study identifier | ALA-AK-CT002, 2007-006854-24 | |
| Design | Randomized, observer blind, multinational, comparator and placebo-controlled parallel-group (3:3:1 ratio) phase III study | |
| | Duration of main phase: | 12 weeks after 1st photodynamic therapy (PDT) |
| | Duration of Run-in phase: | not applicable |
| | Duration of Extension phase: | 12 weeks after 2nd PDT |
| Hypothesis | Superiority of BF-200-ALA over placebo and non-inferiority of BF-200-ALA to Metvix | |
| Treatments groups | BF-200-ALA | BF-200-ALA: 248 |
| | Placebo | Placebo: 76 |
| | Metvix | Metvix : 247 |

| | | | |
|---|---|---|---|
| Endpoints and definitions | **Primary endpoint:** Overall subject complete response assessed 12 weeks after the last PDT | Complete responder rate | An overall complete responder was defined as a subject in whom all treated lesions were cleared after the last PDT. |
| | **Secondary endpoint:** Actinic Keratosis (AK) lesion clearance | Complete lesion response rate | Lesion complete response (completely cleared individual lesions) assessed 12 weeks after the last PDT. |
| Database lock | 7 December 2009 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Intent to treat (ITT, for the comparison of BF-200-ALA *vs.* placebo) and per protocol (PP, BF-200-ALA *vs.* Metvix).<br>12 weeks after last PDT | | | |
| Descriptive statistics and estimate variability | Treatment group | BF-200-ALA | Placebo | Metvix |
| | Number of subjects (ITT) | 248 | 76 | 246 |
| | Complete responder rate (proportion responders) | 78.2% | 17.1% | 64.2% |
| | 95% CI | (72.6, 83.2) | (9.4, 27.5) | (57.9, 70.2) |
| | Number of subjects (PP) | 238 | 65 | 236 |
| | Complete responder rate (proportion responders) | 79.4 | 20.0 | 65.3 |
| | 95% CI | (73.7, 84.4) | (11.1, 31.8) | (58.8, 71.3) |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint (Complete responder rate, ITT) | Comparison groups | BF-200-ALA *vs*. placebo |
| | | Difference in proportions (BF-200-ALA -placebo) | 61.1% |
| | | 95% CI two-sided | (51.2, 71.0) |
| | | P-value (Chi-square test) | *P*<0.0001 |
| | Primary endpoint (Complete responder rate, PP) | Comparison groups | BF-200-ALA v.s. Metvix |
| | | Difference in proportions (BF-200-ALA -Metvix) | 14.0% |
| | | 95% CI two-sided | [6.0; Inf] |
| | | P-value (Chi-square test, 2-sided, alpha=5%) | .0006 |

**Table 15. Summary of Efficacy for trial ALA-AK-CT003**

| | | | | |
|---|---|---|---|---|
| **Title:** A Randomized, Double-Blind, Phase III Multi-Center Study evaluating the safety and efficacy of BF-200 ALA versus Placebo in the treatment of actinic keratosis when using photodynamic therapy | | | | |
| Study identifier | ALA-AK-CT003, 2007-003371-39 | | | |
| Design | Randomized, doubled-blind, placebo-controlled, inter-individual, 2-armed, multicenter phase III study (verum/placebo ratio of 2:1) | | | |
| | Duration of main phase: | | 12 weeks after 1st photodynamic therapy (PDT) | |
| | Duration of Run-in phase: | | not applicable | |
| | Duration of Extension phase: | | 12 weeks after 2nd PDT | |
| Hypothesis | Superiority of BF-200-ALA over placebo | | | |
| Treatments groups | BF-200-ALA | | BF-200-ALA:81 | |
| | Placebo | | Placebo:41 | |
| Endpoints and definitions | **Primary endpoint:** AK Clearance Rate (CR) | Total clearance rate | The number of subjects with complete remission of all AK lesions in the target area(s) assessed 12 weeks after the last PDT. | |
| Database lock | | | | |
| **Results and Analysis** | | | | |
| **Analysis description** | **Primary Analysis** | | | |
| Analysis population and time point description | The analysis of the efficacy parameter was performed for the full analysis set (FAS)<br>12 weeks after last PTD | | | |
| Descriptive statistics and estimate variability | Treatment group | BF-200-ALA | placebo | |
| | Number of subjects (FAS) | 80 | 40 | |
| | Total clearance rate (proportion responders) | 66.3% | 12.5% | |
| | 95% CI | (54.8, 76.4) | (4.2, 26.8) | |
| Effect estimate per comparison | Primary endpoint (Total clearance rate, FAS) | Comparison groups | BF-200-ALA v.s. placebo | |
| | | A Cochran-Mantel-Haenszel test statistic | 32.3619 | |
| | | 95% CI | Not applicable | |
| | | P-value | P<.0001 | |

## Analysis performed across trials (pooled analyses and meta-analysis)

No analyses across trials were submitted.

## Clinical studies in special populations

No studies have been conducted in special populations.

## Supportive studies

No supportive studies have been submitted.

## 2.5.3 Discussion on clinical efficacy

### Design and conduct of clinical studies

The statistical methods used for the phase III studies are in general considered appropriate. Many aspects of the statistical methods are similar between the studies. Missing data are not an issue due to the low number of protocol violations and drop-outs from the studies.

Demographics were balanced between placebo and BF-200 ALA 10% in terms of Gender, race, age, height, weight, BMI, duration of AK lesions, severity and previous treatment in both pivotal studies.

Study ALA-AK-CT002 was designed as three arm study with Ameluz 10%, placebo and Metvix as approved active treatment in the treatment arms. Due to formulation differences in the active arms the study was conducted as observer blinded and this approach is considered acceptable.

Study ALA-AK-CT002 showed superiority of Ameluz 10% compared to placebo and non-inferiority of Ameluz 10% compared to Metvix in terms of overall subject complete response assessed 12 weeks after the last PDT.

Study ALA-AK-CT003 showed superiority of BF-200-ALA over placebo in terms of AK Clearance Rate (CR).

Data exceeding 12 months are not available; therefore a comparison of the long term results with other established treatment modalities is not possible at present. However, this is general an uncertainty for PDT and not only for Ameluz treatment.

## 2.5.4 Conclusions on the clinical efficacy

Overall, the efficacy results are considered compelling enough to establish the clinical efficacy of the product.

## *2.6 Clinical safety*

The safety profile was based on the three clinical trials with Ameluz (ALA-AK-CT1001, ALA-AK-CT002 and ALA-AK-CT003) and a literature survey on the safety of topical treatments with other ALA or MAL formulations.

### Patient exposure

Safety data for Ameluz 10% have been derived from studies which were completed and reported as of cut-off date August 30th, 2010 (Table 16).

**Table 16. Overview of clinical studies of phase II and phase III completed as of cut off-date August 30th, 2010**

| Study details Phase / Study Number | Comparator | Subjects randomized (n) | Safety population (n) | Subjects on BF-200 ALA 10% (n) |
|---|---|---|---|---|
| Phase II | | | | |
| ALA-AK-CT001 | Placebo | 105 | 105 | 28 |
| Phase III | | | | |
| ALA-AK-CT002 | Placebo, Metvix® | 571 | 570 | 248 |
| ALA-AK-CT003 | Placebo | 122 | 122 | 81 |
| Total | | 798 | 797 | 357 |

In ALA-AK-CT002 the safety population was defined as all subjects treated at least once with investigational product.

In ALA-AK-CT003 the safety population was defined as all randomized subjects who received treatment with study medication (independent whether verum or placebo). Within the safety population a subject was, in case such differences occurred, classified according to the treatment actually received rather than to the treatment assigned by randomization.

In the phase II and phase III clinical trial program, the safety population comprised of 797 patients, 357 subjects were exposed to treatment with BF-200 ALA 10% nanoemulsion gel (Table 17). In total, 2114 AK lesions received PDT in this population.

**Table 17. Patient exposure to BF-200 ALA**

| Phase<br>Study number<br>Treatment group | Subjects exposed<br>(n) | Number of<br>AK lesions treated<br>(n) |
|---|---|---|
| **Phase II**<br>**ALA-AK-CT001** | | |
| BF-200 ALA 1% | 25 | 128 |
| BF-200 ALA 3% | 25 | 134 |
| BF-200 ALA 10% | 28 | 147 |
| Placebo | 27 | 135 |
| **Phase III**<br>**ALA-AK-CT002** | | |
| BF-200 ALA 10% | 248 | 1504 |
| Metvix® | 246 | 1557 |
| Placebo | 76 | 490 |
| **Phase III**<br>**ALA-AK-CT003** | | |
| BF-200 ALA 10% | 81 | 463 |
| Placebo | 41 | 225 |

The clinical studies contain demographic variables from a large study population and reflect the typical characteristics of subjects undergoing PDT for AK lesions. Limitations due to the criteria as defined in the respective study protocols were applicable for subjects with known hypersensitivity to ALA, current immunosuppressive therapy, porphyria, hypersensitivity to porphyrins, photodermatoses, inherited or acquired coagulation defects, clinically significant/unstable medical conditions, other malignant or benign tumours of the skin within the treatment area, women of child-bearing potential without reliable contraception, and pregnant or breast-feeding women.

The safety population of confirmatory studies comprised a wide range of body weights and also included a sufficient number of subjects older than 65 years (Placebo treated patients: 98, Ameluz 10% treated patients: 262). With respect to race it was a Caucasian population only. No relevant differences were observed between the two confirmatory studies with respect to demographic variables.

## Adverse events

The incidence of adverse reactions in the population exposed to treatment with Ameluz (357 subjects) is listed below. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), and not known (cannot be estimated from the available data).

**Table 18. Overview of adverse reactions**

| System organ class | Frequency | Adverse reaction |
|---|---|---|
| Infections and infestations | Uncommon | At application site: Rash pustular |
| Psychiatric disorders | Uncommon | Nervousness |
| Nervous system disorders | Common | Headache |
| | Uncommon | At application site: Dysaesthesia |
| Eye disorders | Uncommon | At application site: Eyelid oedema |
| Skin and subcutaneous disorders | Common | At application site: Skin tightness |
| | Uncommon | At application site: Dry skin, petechiae, hyperkeratosis |
| General disorders and administration site conditions | Very common | At application site: Irritation, erythema, pain, pruritus, oedema, exfoliation, scab, induration |
| | Common | At application site: Vesicles, paraesthesia, hyperalgesia, erosion, warmth |
| | Uncommon | At application site: Bleeding, discomfort, discharge, discoloration, ulcer |
| | | Not at application site: Chills, feeling hot, pyrexia, pain |
| Injury, poisoning and precedural complications | Uncommon | Wound secretion |

**Study ALA-AK-CT001**

An overview of adverse events (AEs) is shown in table 19.

**Table 19. Phase II study ALA-AK-CT001-Overview of treatment-emergent adverse events (population valid for safety analysis)**

| Adverse event type | Placebo n=27 % | BF-200 ALA 1% n=25 % | BF-200 ALA 3% n=25 % | BF-200 ALA 10% n=28 % |
|---|---|---|---|---|
| Any treatment-emergent AE | 21 (77.8%) | 21 (84.0%) | 23 (92.0%) | 28 (100.0%) |
| Any drug-related treatment-emergent AE | 21 (77.8%) | 20 (80.0%) | 23 (92.0%) | 27 (96.4%) |
| Any AE resulting in permanent discontinuation of study drug | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Any treatment-emergent SAE | 1 (3.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Any drug-related treatment-emergent SAE | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Any death | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

Abbreviations: AE=adverse event; SAE=serious adverse event

The majority of adverse events were non-serious application site disorders associated with PDT, that occur in 77.8% of subjects receiving placebo, 80% receiving Ameluz 1%, 92.0% receiving Ameluz 3%, and 96.4% receiving Ameluz 10%.

The most common TEAE other than application site disorders was nasopharyngitis occurring in 3 subjects receiving Ameluz 10%. All other events did not occur in more than 1 subject in any treatment group.

All drug-related adverse events were non-serious application site disorders associated with PDT. Application site erythema was the most frequently reported application site disorder. Table 20 presents the most frequent drug-related TEAEs.

**Table 20. Phase II study ALA-AK-CT-001-Incidence of drug-related treatment-emergent adverse events (population valid for safety analysis)**

| Primary system organ class<br>Preferred term | Placebo<br>n=27 | BF-200 ALA<br>1%<br>n=25 | BF-200 ALA<br>3%<br>n=25 | BF-200 ALA<br>10%<br>n=28 |
|---|---|---|---|---|
| Any subject with drug-related adverse events | 21 (77.8%) | 20 (80.0%) | 23 (92.0%) | 27 (96.4%) |
| General disorders and administration site conditions | | | | |
| Any event | 21 (77.8%) | 20 (80.0%) | 23 (92.0%) | 27 (96.4%) |
| Application site edema | 0 (0.0%) | 1 (4.0%) | 5 (20.0%) | 4 (14.3%) |
| Application site erosion | 0 (0.0%) | 0 (0.0%) | 1 (4.0%) | 0 (0.0%) |
| Application site erythema | 21 (77.8%) | 17 (68.0%) | 23 (92.0%) | 22 (78.6%) |
| Application site exfoliation | 0 (0.0%) | 1 (4.0%) | 0 (0.0%) | 0 (0.0%) |
| Application site induration | 0 (0.0%) | 2 (8.0%) | 1 (4.0%) | 1 (3.6%) |
| Application site irritation | 6 (22.2%) | 14 (56.0%) | 13 (52.0%) | 14 (50.0%) |
| Application site pain | 2 (7.4%) | 8 (32.0%) | 6 (24.0%) | 11 (39.3%) |
| Application site pruritus | 3 (11.1%) | 7 (28.0%) | 4 (16.0%) | 9 (32.1%) |
| Application site reaction | 1 (3.7%) | 3 (12.0%) | 4 (16.0%) | 10 (35.7%) |
| Application site scab | 1 (3.7%) | 2 (8.0%) | 1 (4.0%) | 2 (7.1%) |
| Application site vesicles | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (3.6%) |
| Application site warmth | 2 (7.4%) | 3 (12.0%) | 1 (4.0%) | 3 (10.7%) |

**Study ALA-AK-CT002**

An overview of TEAEs is presented in table 21.

**Table 21. Overview of treatment-emergent adverse events in subjects (safety population)**

| AE category | No. (%) subjects | | | | | |
|---|---|---|---|---|---|---|
| | Placebo (N=76) | | BF-200 ALA (N=248) | | Metvix® (N=246) | |
| Any TEAE | 55 | (72.4) | 239 | (96.4) | 241 | (98.0) |
| Related TEAE* | 50 | (65.8) | 236 | (95.2) | 240 | (97.6) |
| Any serious TEAE | 3 | (3.9) | 11 | (4.4) | 10 | (4.1) |
| Related serious TEAE* | 0 | | 0 | | 0 | |
| TEAEs resulting in death | 0 | | 0 | | 0 | |
| TEAEs leading to study withdrawal | 0 | | 2 | (0.8) | 2 | (0.8) |
| Related TEAEs leading to study withdrawal | 0 | | 1 | (0.4) | 0 | |
| TEAEs rated as local skin reaction | 35 | (46.1) | 200 | (80.6) | 197 | (80.1) |
| Related TEAEs rated as local skin reaction | 35 | (46.1) | 200 | (80.6) | 197 | (80.1) |
| TEAEs rated as discomfort during PDT | 31 | (40.8) | 221 | (89.1) | 230 | (93.5) |
| Related TEAEs rated as discomfort during PDT | 31 | (40.8) | 221 | (89.1) | 230 | (93.5) |

Table 11.3.1.1

*Related = all possibly, probably or definitely related TEAEs

The majority of TEAEs were non-serious application site disorders associated with PDT, which occurred in 64.5% of subjects receiving placebo, 94.8% receiving Ameluz 10%, and 96.7% receiving Metvix. Adverse events were more frequent in subjects receiving active treatment than in those receiving placebo.

The table 22 presents the most frequent drug-related TEAEs by MedDRA system organ class and preferred term.

**Table 22. Phase III study ALA-AK-CT002 – Incidence of drug-related, treatment-emergent adverse events occurring in ≥4 subjects in any treatment group (population valid for safety analysis)**

| Primary system organ class<br>Preferred term | Placebo<br>n=76 | BF-200 ALA<br>10%<br>n=248 | Metvix®<br>n=246 |
|---|---|---|---|
| Any subject with drug-related adverse events | 50 (65.8%) | 236 (95.2%) | 240 (97.6%) |
| General disorders and administration site conditions | | | |
| Any event [a] | 49 (64.5%) | 235 (94.8%) | 238 (96.7%) |
| Application site discharge | 0 (0.0%) | 2 (0.8%) | 5 (2.0%) |
| Application site edema | 1 (1.3%) | 62 (25.0%) | 61 (24.8%) |
| Application site erosion | 1 (1.3%) | 8 (3.2%) | 6 (2.4%) |
| Application site erythema | 31 (40.8%) | 198 (79.8%) | 199 (80.9%) |
| Application site exfoliation | 5 (6.6%) | 44 (17.7%) | 44 (17.9%) |
| Application site hypersensitivity[b] | 0 (0.0%) | 10 (4.0%) | 3 (1.2%) |
| Application site induration | 0 (0.0%) | 24 (9.7%) | 21 (8.5%) |
| Application site irritation | 25 (32.9%) | 219 (88.3%) | 222 (90.2%) |
| Application site pain | 19 (25.0%) | 175 (70.6%) | 179 (72.8%) |
| Application site paresthesia | 2 (2.6%) | 17 (6.9%) | 18 (7.3%) |
| Application site pruritus | 6 (7.9%) | 59 (23.8%) | 60 (24.4%) |
| Application site scab | 2 (2.6%) | 27 (10.9%) | 30 (12.2%) |
| Application site vesicles | 1 (1.3%) | 22 (8.9%) | 23 (9.3%) |
| Nervous system disorders | | | |
| Any event [a] | 0 (0.0%) | 6 (2.4%) | 6 (2.4%) |
| Headache | 0 (0.0%) | 5 (2.0%) | 6 (2.4%) |
| Skin and subcutaneous tissue disorders | | | |
| Any event [a] | 3 (3.9%) | 26 (10.5%) | 22 (8.9%) |
| Erythema | 1 (1.3%) | 7 (2.8%) | 5 (2.0%) |
| Pruritus | 0 (0.0%) | 5 (2.0%) | 1 (0.4%) |
| Scab | 1 (1.3%) | 3 (1.2%) | 4 (1.6%) |
| Skin exfoliation | 1 (1.3%) | 17 (6.9%) | 15 (6.1%) |

a: Data for all treatment emergent adverse events in this category are given. Details are only shown when occurring in ≥4 subjects in any treatment group.
b: faulty classification in one clinical center, should be hyperalgesia

Non-serious application site irritation, application site erythema, and application site pain were the most frequently reported application site disorders.

The most common drug-related TEAE other than application site disorders or skin disorders was headache (placebo 0.0%, Ameluz 2.0%, Metvix 2.4%).

The more intense and higher number of adverse reactions correlated when patients were irradiated with the narrow spectrum device (Table 23).

**Table 23. Main adverse effects achieved by different lamp devices in Study AL-AK-CT0002**

| Light source | Drug | Application site Erythema (%) | | | Application site pain (%) | | |
|---|---|---|---|---|---|---|---|
| | | mild | moderate | severe | mild | moderate | severe |
| Narrow spectrum | BF-200 ALA10% | 13 | 43 | 35 | 12 | 33 | 46 |
| | Metvix® | 18 | 43 | 29 | 12 | 33 | 48 |
| Broad spectrum | BF-200 ALA10% | 32 | 29 | 6 | 17 | 25 | 5 |
| | Metvix® | 31 | 33 | 3 | 20 | 23 | 8 |

**Study ALA-AK-CT003**

The incidence of AEs in Study ALA-AK-CT003 is presented in table 24.

**Table 24. Incidence of Adverse events**

| | Treatment group | |
|---|---|---|
| | BF-200 ALA<br>N=81<br>N (%) | Placebo<br>N=41<br>N (%) |
| Subjects with any AE | 78 (96.3) | 20 (48.8) |
| Subjects with severe AE | 13 (16.0) | 1 (2.4) |
| Subjects discontinued due to an AE | 0 | 0 |
| Subjects with related AE* | 78 (96.3) | 16 (39.0) |
| Subjects with SAE | 0 | 2 (4.9%) |

* 'Probably related', 'Possibly related' or 'Related' AEs were counted as related AEs.

The majority of TEAEs were non-serious application site disorders associated with PDT, which occurred in 39.0% of subjects receiving placebo and in 96.3% of those receiving Ameluz 10%.

TEAEs were mainly of mild to moderate intensity; the overall incidences of events with severe intensity were 2.4% (placebo) and 16.0% (Ameluz 10%).

The table 25 presents the most frequent drug-related TEAEs by MedDRA system organ class and preferred term.

**Table 25. Phase III study ALA-AK-CT003 – Incidence of drug-related, treatment-emergent adverse events (population valid for safety analysis)**

| Primary system organ class<br>Preferred term | Placebo<br>n=41 | BF-200 ALA 10%<br>n=81 |
|---|---|---|
| Any subject with any drug-related adverse events | 16 (39.0%) | 78 (96.3%) |
| General disorders and administration site conditions | | |
| Any event | 16 (39.0%) | 78 (96.3%) |
| Application site discomfort | 0 (0.0%) | 1 (1.2%) |
| Application site edema | 1 (2.4%) | 32 (39.5%) |
| Application site erythema | 15 (36.6%) | 72 (88.9%) |
| Application site induration | 0 (0.0%) | 12 (14.8%) |
| Application site irritation | 10 (24.4%) | 70 (86.4%) |
| Application site pain | 4 (9.8%) | 44 (54.3%) |
| Application site pruritus | 0 (0.0%) | 27(33.3%) |
| Application site reaction | 2 (4.9%) | 9 (11.1%) |
| Application site scab | 0 (0.0%) | 1 (1.2%) |
| Application site vesicles | 0 (0.0%) | 1 (1.2%) |
| Pyrexia | 0 (0.0%) | 1 (1.2%) |
| Infections and infestations | | |
| Any event | 0 (0.0%) | 2 (2.5%) |
| Application site pustules | 0 (0.0%) | 1 (1.2%) |
| Nasopharyngitis[a] | 0 (0.0%) | 1 (1.2%) |
| Nervous system disorders | | |
| Any event | 0 (0.0%) | 1 (1.2%) |
| Headache | 0 (0.0%) | 1 (1.2%) |
| Skin and subcutaneous tissue disorders | | |
| Any event | 0 (0.0%) | 1 (1.2%) |
| Pruritus | 0 (0.0%) | 1 (1.2%) |

[a] Patient suffered from a cold starting 69 days after the PDT and lasting for 8 days. Classified as "possibly related" by the investigator.

Nearly all drug-related adverse events were non-serious application site disorders associated with PDT. Application site erythema, application site irritation, and application site pain were the most frequently reported application site disorders. Incidence rates were 36.6% (placebo) and 88.9% (Ameluz 10%) for application site erythema; 24.4% (placebo) and 86.4% (Ameluz 10%) for application site irritation; and 9.8% (placebo) and 54.3% (Ameluz 10%) for application site pain.

Other drug-related treatment-emergent adverse events were rare and occurred in the Ameluz 10% group only.

The more intense and higher number of adverse reactions observed when patients were irradiated with the narrow spectrum device (Table 26).

**Table 26. Main adverse effects achieved by different lamp devices in Study AL-AK-CT0003**

| Light source | Drug | Application site Erythema (%) | | | Application site pain (%) | | |
|---|---|---|---|---|---|---|---|
| | | mild | moderate | severe | mild | Moderate | severe |
| Narrow | BF-200 ALA10%® | 26 | 67 | 7 | 30 | 35 | 16 |
| Broad | BF-200 ALA10%® | 47 | 19 | 0 | 35 | 14 | 0 |

## Serious adverse event/deaths/other significant events

### Serious adverse events

Only 1 serious TEAE was reported in Study ALA-AK-CT001. This concerned a subject of the placebo group who experienced 2 syncopes about 8 weeks after receiving PDT. The event resolved and was considered unrelated to study drug.

No related serious TEAEs were reported in Study ALA-AK-CT002. No TEAEs resulting in death were reported during the clinical part of the study. Overall frequencies of serious TEAEs were low and similar in the Metvix and Ameluz 10% groups (10 [4.1%] and 11 [4.4%] subjects, respectively); and were 3 (3.9%) subjects in the placebo group. The following serious TEAEs were reported in 2 or more subjects: arrhythmia (1 subject in the placebo group and 1 in the Ameluz10% group), contusion (1 in the Metvix and 1 in the Ameluz 10% group) and cerebrovascular accident (both in the Metvix group). All of the serious TEAEs were assessed as not related to study medication by the investigator.

During the follow-up study, 10 serious TEAEs were reported in 8 subjects; 3 subjects were treated with Ameluz 10%, 5 subjects received Metvix. Four SAEs were fatal. The serious TEAEs occurred between about 6 weeks after the last PDT (subject 115/38) and about 1 year after the last PDT (subjects 120/31 and 102/06). None of the serious adverse events were assessed as drug-related.

Study ALA-AK-CT003 had 2 serious TEAEs that occurred during the study in 2 subjects receiving placebo. No events occurred in the Ameluz 10% group. None of the serious TEAEs were assessed as drug-related.

**Deaths**

No death occurred in the phase II trial. No death occurred in the phase III trials during the actual study duration. In study ALA-AK-CT002, 4 subjects died during the follow-up period, one in the Ameluz 10% group and 3 in the Metvix group. All deaths were considered unrelated to the study medication.

## Laboratory findings

In all studies, laboratory monitoring showed no clinically relevant drug-related changes.

## Safety in special populations

**Geriatric use**

Altogether 284 patients >65 years were treated with Ameluz 10%, 262 of whom participated in the pivotal studies (Table 27).

**Table 27. Geriatric population treated with BF-200 ALA 10% (safety population)**

| Patients' age | ≤65 years<br>n (%) | >65 years<br>n (%) | Total<br>n (%) |
|---|---|---|---|
| ALA-AK-CT001 | 6 (21.4%) | 22 (78.6%) | 28 (100%) |
| ALA-AK-CT002 | 55 (22.2%) | 193 (77.8%) | 248 (100%) |
| ALA-AK-CT003 | 12 (14.8%) | 69 (85.2%) | 81 (100%) |
| Total n (%) | 73 (20.4%) | 284(79.6%) | 357 (100%) |

When the safety data of the 2 pivotal studies were analyzed in age groups ≤ 65, >65 to 75 and >75 years, no meaningful difference was identified with respect to treatment emergent adverse events. As the adverse events identified were usually non-serious application site reactions no pooled analysis was performed for the studies.

**Pregnancy and lactation**

Animal reproduction studies have not been conducted with Ameluz 10%. It is also not known whether Ameluz 10% can cause foetal harm when administered topically to a pregnant woman or can affect reproductive capacity.

Literature experience on the potential influence of ALA on pregnancy is described in a case report of a patient suffering from porphyria described a porphyric attack precipitated by pregnancy. Pregnancy continued to full term with spontaneous delivery. The neonate was apparently normal, despite high levels of ALA in maternal plasma (up to 12 µmol/L) throughout gestation and high level of ALA in the cord blood.

There are no data from the use of ALA in pregnant women. Animal studies do not indicate reproductive toxicity. As a precautionary measure, Ameluz 10% is not recommended during pregnancy and in women of childbearing potential not using contraception. This is reflected in section 4.6 of the SmPC.

The levels of ALA or its metabolites in the milk of subjects treated with Ameluz 10% have not been measured. Because many drugs are excreted in human milk, caution should be exercised when Ameluz 10% is administered to a nursing woman. As a precautionary measure, breast feeding should be interrupted for 12 hours (corresponding to more than five half-lives of ALA following systemic administration) following a PDT treatment with the BF- 200 ALA 10% gel. This is reflected in section 4.6 of the SmPC.

## Safety related to drug-drug interactions and other interactions

Not investigated.

## Discontinuation due to adverse events

In study ALA-AK-CT002, discontinuation rates for any reason were higher in the placebo group (10.5%) than in the two active groups (both 2.8%). In the other 2 studies, no relevant differences were observed between placebo and Ameluz 10% (Table 28).

**Table 28. Study subject withdrawals in controlled studies (safety population)**

| Phase<br>Study number<br>Reason for withdrawal | Placebo<br>n (%) | BF-200 ALA 10%<br>n (%) | Metvix®<br>n (%) |
|---|---|---|---|
| **ALA-AK-CT001** | 27 (100.0%) | 28 (100.0%) | N/A |
| Premature termination total | 0 (0.0%) | 1 (3.6%) | N/A |
| Scheduled surgery | 0 (0.0%) | 1 (3.6%) | N/A |
| **ALA-AK-CT002** | 76 (100.0%) | 248 (100.0%) | 246 (100.0%) |
| Premature termination total | 8 (10.5%) | 7 (2.8%) | 7 (2.8%) |
| Adverse event | 0 (0.0%) | 2 (0.8%) | 2 (0.8%) |
| Lack of efficacy | 2 (2.6%) | 0 (0.0%) | 0 (0.0%) |
| Lost to follow-up | 1 (1.3%) | 1 (0.4%) | 0 (0.0%) |
| Protocol violation | 0 (0.0%) | 0 (0.0%) | 2 (0.8%) |
| Subject's decision | 4 (5.3%) | 4 (1.6%) | 3 (1.2%) |
| Sponsor's request due to violation of an exclusion criterion | 1 (1.3%) | 0 (0.0%) | 0 (0.0%) |
| **ALA-AK-CT003** | 41 (100.0%) | 81 (100.0%) | N/A |
| Premature termination total | 4 (9.8%) | 4 (4.9%) | N/A |
| Protocol deviation | 0 (0.0%) | 1 (1.2%) | N/A |
| Consent withdrawn | 4 (9.8%) | 3 (3.7%) | N/A |

The rate of discontinuation during the follow-up phases of Studies ALA-AK-CT002 and ALA-AK-CT003 were similar in the treatment groups (5.3%, 3.2% and 3.7% in ALA-AK-CT002 for placebo, Ameluz 10% and Metvix and in ALA-AK-CT003 13.5% and 9.1% for placebo and Ameluz 10%, respectively). The main reason for withdrawal was lost to follow up (Table 29).

**Table 29. Study subject withdrawals in follow-up studies**

| Phase<br>Study number<br>Reason for withdrawal | Placebo<br>n (%) | BF-200 ALA<br>10%<br>n (%) | Metvix®<br>n (%) |
|---|---|---|---|
| **ALA-AK-CT002** | 76 (100.0%) | 248 (100.0%) | 246 (100.0%) |
| Completion of follow-up | 64 (84.2% | 233 (94.0%) | 231 (93.9%) |
| Premature termination total | 4 (5.3%) | 8 (3.2%) | 9 (3.7%) |
| Adverse event | 0 (0.0% | 0 (0.0%) | 1 (0.4%) |
| Death | 0 (0.0% | 1 (0.4%) | 3 (1.2%) |
| Lost to follow-up | 3 (3.9%) | 1 (0.4%) | 3 (1.2%) |
| Subject's decision | 1 (1.3%) | 3 (1.2%) | 2 (0.8%) |
| Missing reason | 0 (0.0%) | 3 (1.2%) | 0 (0.0%) |
| **ALA-AK-CT003** | **41 (100.0%)** | **81 (100.0%)** | N/A |
| Completion of follow-up | 32 (86.5%) | 70 (90.9%) | N/A |
| Premature termination total | 5 (13.5%) | 7 (9.1%) | N/A |
| Lost to follow-up | 4 (10.8%) | 6 (7.8%) | N/A |
| Subject's decision | 1 (2.7%) | 1 (1.3%) | N/A |

Abbreviations: N/A = not applicable

## Post marketing experience

Not available.

## 2.6.1 Discussion on clinical safety

High rates of application site disorders were seen with treatment with BF 200-ALA which is expected based on the known mechanism of action as a locally acting treatment (PDT) for AK lesions.

The most common adverse events reported were erythema, irritation, oedema and pain. Similar application site disorders TEAE rates were seen between BF-200-ALA vs Metvix and it therefore appears to have a similar safety profile. However, a single patient discontinued study participation due to the occurrence of TEAE following treatment with Ameluz 10% (non-serious application site pain and non-serious application site irritation (both severe) after treatment in PDT1).

In ALA AK CT002 study rates of severe TEAEs were similar in the Ameluz 10% and Metvix treatment groups, 41.9% and 41.5% respectively.

Most adverse reactions occur during illumination or shortly afterwards. The symptoms are usually of mild or moderate intensity, and last for 1 to 4 days in most cases; in some cases, however, they may persist for 1 to 2 weeks or even longer. In rare cases, the adverse reactions may require interruption or discontinuation of the illumination.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics (SmPC).

The incidence of adverse events was higher in the first PDT versus a subsequent treatment. However not all patients required a second PDT treatment. It could be that the cohort requiring a second treatment were less likely to experience an adverse event rather than that the likelihood of an adverse event fell with repeated treatment.

There does not appear to be strong evidence showing any relationship between age and the frequency of application site disorders

There appears to be a relationship between application site disorders and narrow spectrum light source. As a higher incidence of applications site reactions occurred for first and second PDT sessions in patients receiving narrow beam versus broad beam light sources.

The cohort of patients included in the clinical trials programme excluded patients who were immunosuppressed or receiving immunosuppressant drugs or with a confirmed diagnosis of HIV. People who are immune-suppressed are more likely to undergo malignant transformation of their actinic keratosis and therefore more likely to need treatment to prevent transformation.

No experience exists for the treatment of basal cell carcinoma and Bowens's disease, which should therefore not be treated with the product.

Furthermore there is no experience of treating severe actinic keratoses or lesions which are pigmented or highly infiltrating and treating actinic keratosis lesions in patients with dark brown or black skin (skin sun sensitivity type V or VI according to Fitzpatrick).

The success and assessment of treatment may be impaired if the treated area is affected by the presence of skin diseases (skin inflammation, located infection, psoriasis, excema, and benign or malignant skin cancers) as well as tattoos. No experience exists with these situations.

Any UV-therapy should be discontinued before treatment. As a general precaution, sun exposure on the treated lesion sites and surrounding skin should be avoided for approximately 48 hours following treatment.

Ameluz is contraindicated in patients with porphyria and known photodermatoses of varying pathology and frequency, e.g. metabolic disorders such as aminoaciduria, idiopathic or immunological disorders such as polymorphic light reaction, genetic disorders such as xeroderma pigmentosum, and diseases precipitated or aggravated by exposure to sun light such as lupus erythematoides or phemphigus erythemtoides.

Overdose following topical administration is unlikely and has not been reported in clinical studies. If Ameluz is accidentally ingested, systemic toxicity is unlikely. Protection from sun light exposure for 48 hours and observation are nevertheless recommended.

### 2.6.2 Conclusions on the clinical safety

The safety profile of BF-ALA-200 is considered acceptable. Overall the majority of adverse events were localised skin reactions, erythema, pain, oedema and irritation which were usually mild to moderate in severity and self limiting.

The more intense and higher number of adverse reactions correlated with the higher efficacy rates observed when patients were irradiated with the narrow spectrum device.

The adverse events recorded appear to be consistent between the studies and are expected as a localised form of PDT treatment of AK lesions.

## *2.7 Pharmacovigilance*

### Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### Risk Management Plan

The applicant submitted a risk management plan.

**Table 30**: **Summary of the risk management plan**

| **Safety concern** | **Proposed pharmacovigilance activities (routine and additional)** | **Proposed risk minimization activities (routine and additional)** |
|---|---|---|
| Important identified risk:<br>• Application site reactions<br>Important potential risks:<br>• Severe application site reaction in combination with photosensitizing medication or in patients with photodermatoses<br>• Application site hypersensitivity<br>• Rate of infections/ infestations: nasopharyngitis<br>• Recurrence rate in treated lesions | Routine pharmacovigilance activities are considered sufficient and no further actions are required.<br><br>The use in elderly patients and the respective safety profile will be discussed as part of the overall safety evaluation in post authorization PSURs<br><br>Case reports associated with potential risks will be evaluated as events of special interest in the PSUR. | Important identified and potential risks are adequately described in the product information.<br><br>Application site reactions are described in section 4.8 of the SmPC.<br><br>Hypersensitivity to ALA, porphyrins and excipients is listed as contraindication in section 4.3 of the SmPC.<br><br>Photodermatoses and porphyria are listed as contra-indication in section 4.3 of the SmPC.<br><br>Risks associated with concomitant treatment with photosensitizing medication are described in section 4.4 of the SmPC.<br><br>None for rate of infections/infestations: nasopharyngitis.<br><br>None for recurrence rate in treated lesions. |
| Important missing information:<br>• Treatment of patients with immunosuppression<br>• Safety in patients with skin type I | Routine pharmacovigilance activities are considered sufficient and no further actions are required.<br><br>Case reports in patients receiving immune-suppression and in patients with skin type I will be evaluated as events of special interest in the PSUR. | Lack of experience in the immunosuppressed patient group is described in section 4.4 of the SmPC.<br><br>None for safety in patients with skin type I. |

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

## *2.8 User consultation*

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

# 3. Benefit-Risk Balance

## *Benefits*

## Beneficial effects

Two pivotal trials were submitted in support of the efficacy of Ameluz in patients with actinic keratosis of mild to moderate intensity on the face and scalp.

In study ALA-AK-CT002 the 61.1% (95% CI: 51.2; 71.0) difference on complete clearance 12 weeks after the last PDT treatment between the two treatment groups was statistically significant ($p<0.0001$), demonstrating superiority of Ameluz to placebo. This effect was further substantiated by results in the main secondary efficacy endpoint: total clearance rates were higher for Ameluz (90.4%) compared to Metvix (83.2%) and placebo (37.1%).

In study ALA-AK-CT003, 53 (66.3%) subjects in the Ameluz group and 5 (12.5%) in the placebo group showed complete clearance 12 weeks after the last PDT treatment. In the PP population, 49 (63.6%) subjects in the Ameluz group and 4 (10.8%) in the placebo group showed complete clearance. In both analysis, the difference between the 2 treatment groups (53.8% points in the FAS population and 52.8 % in the PP population) was statistically significant ($P<0.0001$) demonstrating superiority of Ameluz to placebo.

This effect supported by the results in the main secondary efficacy endpoint: total lesion clearance was higher for Ameluz (81.1%) compared to placebo (20.9%).

## Uncertainty in the knowledge about the beneficial effects

There are adequate data to assess the beneficial effects of the product. There are no important uncertainties in the knowledge about beneficial effects.

## *Risks*

## Unfavourable effects

The most common adverse events reported were erythema, irritation, oedema and pain. For the majority, the localised skin reactions were mild to moderate, self limiting and recovered after 1 week.

Using a narrow spectrum red light source resulted in a higher rate of skin irritation at the treatment site; however this results also in better efficacy.

## Uncertainty in the knowledge about the unfavourable effects

There are adequate data to assess the unfavourable effects of the product. There are no important uncertainties in the knowledge about unfavourable effects.

## *Benefit-risk balance*

Clinical benefits of Ameluz treatment of actinic keratosis clearly exceed the few and mostly mild adverse effects. With better efficacy and slightly better safety profile than the standard treatment with the licensed comparator product the benefit-risk balance for Ameluz is clearly positive.

### Importance of favourable and unfavourable effects

Complete AK clearance is a relevant clinical endpoint. The results are considered to be robust, consistent, and of clinical relevance.

The safety profile is considered acceptable. Local adverse effects like irritation with erythema and pain were the most predominant unfavourable effects after treatment with Ameluz. In most of the cases, only mild or moderate degree effects which were completely reversible were noted.

### Benefit-risk balance

Clinical benefits of Ameluz treatment of actinic keratosis clearly exceed the few and mostly mild adverse effects. The benefit-risk balance for Ameluz is clearly positive.

# 4. Recommendations

## *Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the risk-benefit balance of Ameluz in the treatment of actinic keratosis is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

## *Conditions or restrictions regarding supply and use*

Medicinal product subject to restricted medical prescription

## *Conditions and requirements of the Marketing Authorisation*

#### *Risk Management System*

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

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